Program and Abstracts

CROI 2015

Conference on Retroviruses and Opportunistic Infections

February 23-26, 2015
Seattle, Washington

IAS–USA
International Antiviral Society–USA

CONTENTS

CROI FOUNDATION ii

IAS–USA ii

CROI 2015 PROGRAM COMMITTEE iii

- Scientific Program Committee iii
- Community Liaison Subcommittee iv

EXTERNAL REVIEWERS v

COMMERCIAL SUPPORT vi

CONFERENCE SCHEDULE OVERVIEW vii

CONVENTION CENTER FLOOR PLANS ix

CONTINUING MEDICAL EDUCATION xii

- Accreditation Statement xii
- Objectives xii
- Statement of Need xii
- CME Credit Information xii
- Claiming CME Credits or a Certificate of Participation xii
- Faculty Financial Disclosure xii
- Drug and Product Disclaimer xii

GENERAL INFORMATION xiii

- Overview xiii
- Americans with Disabilities Act xiii
- Ebola Precautions xiii
- Welcome Reception xiii
- Meals xiii
- Overflow Accommodations for Session Rooms xiv
- USB Flash Drive xiv
- Website xiv
- Webcasts and Podcasts xiv
- Mobile App xiv
- Wi-Fi Access at the Conference xiv
- Badges xiv
- Child Care xiv
- Conference Etiquette xiv

CONFERENCE SERVICES xv

HOTEL INFORMATION xvi

ABSTRACTS xviii

- Scientific Categories xviii
- Abstract Content xviii
- Abstract Review Process xviii
- Common Reasons for Abstract Rejection xviii
- Statistics xviii

EMBARGO POLICY xix

- General xix
- Social Media xix

YOUNG INVESTIGATOR AWARDEES xx

INTERNATIONAL SCHOLARSHIP AWARDEES xxvi

COMMUNITY EDUCATOR SCHOLARSHIP AWARDEES xxvii

ORAL SESSIONS 1

POSTER SESSIONS, BY CATEGORY 22

POSTER LISTINGS, BY CATEGORY 24

ORAL ABSTRACTS 84

POSTER ABSTRACTS 197

DISCLOSURE INFORMATION 652

DISCLOSURE INFORMATION 656

AUTHOR INDEX 660

KEYWORD INDEX 682

© Copyright 2015 IAS–USA/CROI Foundation. All rights reserved.
ISBN # 978-0-692-36902-9

CROI FOUNDATION

The CROI Foundation operates exclusively for the charitable and educational purpose of organizing, promoting, and presenting the Conference on Retroviruses and Opportunistic Infections (CROI).

Roles and Responsibilities of the CROI Foundation Board of Directors

- Works closely with the CROI Scientific Program Committee (CROI PC) and the CROI Secretariat to accomplish the mission of CROI
- Approves nominations for members of the CROI PC and the CROI PC Chair and Vice Chairs
- Ensures that the CROI PC is responsible for the scientific program content of CROI
- Enters into and oversees the partner agreement with the CROI Secretariat
- Has the sole and absolute discretion to veto any policies, procedures, or actions taken or proposed to be taken by the CROI PC or the CROI Secretariat that would pose a substantial risk of preventing the Foundation at any time from qualifying or continuing to qualify as a 501(c)(3) organization or that might cause the loss of such qualification
- Oversees the long-term financial and administrative integrity of CROI

Composition of the CROI Foundation Board of Directors

The Board of Directors comprises current and previous CROI Chairs and Vice Chairs and selected members of the CROI PC.

CROI Foundation Board Members

Constance A. Benson, MD, President
University of California San Diego
San Diego, CA, US

John M. Coffin, PhD, Secretary-Treasurer
Tufts University
Boston, MA, US

Elaine J. Abrams, MD
International Center for AIDS Care and Treatment Programs
Columbia University
New York, NY, US

Susan P. Buchbinder, MD
San Francisco Department of Public Health
University of California San Francisco
San Francisco, CA, US

Judith S. Currier, MD, MsC
University of California Los Angeles
Los Angeles, CA, US

Kevin M. De Cock, MD
Centers for Disease Control and Prevention
Nairobi, Kenya

Scott M. Hammer, MD
Columbia University Medical Center/New York–Presbyterian Hospital
New York, NY, US

John W. Mellors, MD
University of Pittsburgh
Pittsburgh, PA, US

Julie M. Overbaugh, PhD
Fred Hutchinson Cancer Research Center
Seattle, WA, US

Robert T. Schooley, MD
University of California San Diego
San Diego, CA, US

Mario Stevenson, PhD
University of Miami
Miami, FL, US

IAS–USA

The International Antiviral Society–USA is a 501(c)(3) not-for-profit professional education organization. The IAS–USA serves as the Conference Secretariat for CROI.

The mission of the IAS–USA is to improve the treatment, care, and quality of life for people with HIV, hepatitis C virus, or other viral infections through high-quality, relevant, balanced, and needs-oriented education and information for practitioners and scientists who are actively involved in medical care and research.

Executive Director: Donna M. Jacobsen

Address: 425 California Street, Suite 1450
San Francisco, CA 94104-2120

Phone: 415-544-9400

Website: www.iasusa.org

IAS–USA
International Antiviral Society–USA

CROI 2015 PROGRAM COMMITTEE

The Scientific Program Committee (PC) is a team of experts in their given field who volunteer to organize the scientific program for CROI. Members are selected based on their area of scientific expertise and their commitment to the mission of the conference. Initial terms are 3 years; subsequent terms are based on previous participation and interest level. Members are nominated by the PC and approved by the CROI Foundation Board of Directors. The "goodwill ambassadors" of CROI, PC members are also responsible for identifying topics and speakers that will ensure innovative programming; strategic planning; abstract review and program development; and organizing, conducting, and convening workshops, symposia, and special sessions.

Scientific Program Committee

Scott M. Hammer, MD
CROI 2015 Chair
Columbia University Medical Center/New York–Presbyterian Hospital
New York, NY, US

Julie M. Overbaugh, PhD
CROI 2015 Vice Chair
Fred Hutchinson Cancer Research Center
Seattle, WA, US

Susan P. Buchbinder, MD
CROI 2015 Vice Chair
San Francisco Department of Public Health
University of California San Francisco
San Francisco, CA, US

Elaine J. Abrams, MD
ICAP at Columbia University
New York, NY, US

Galit Alter, PhD
Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard University
Boston, MA, US

Constance A. Benson, MD
University of California San Diego
San Diego, CA, US

Bruce J. Brew, MD, MBBS
St. Vincent's Hospital
Sydney, Australia

Ellen G. Chadwick, MD
Northwestern University
Ann and Robert J. Lurie Children's Hospital of Chicago
Chicago, IL, US

Richard E. Chaisson, MD
The Johns Hopkins University
Baltimore, MD, US

John M. Coffin, PhD
Tufts University
Boston, MA, US

Judith S. Currier, MD, MSc
University of California Los Angeles
Los Angeles, CA, US

Kevin M. De Cock, MD
Centers for Disease Control and Prevention
Nairobi, Kenya

Wafaa M. El-Sadr, MD, MPH
ICAP at Columbia University
New York, NY, US

Courtney V. Fletcher, PharmD
University of Nebraska Medical Center College of Pharmacy
Omaha, NE, US

Dana H. Gabuzda, MD
Dana-Farber Cancer Institute and Harvard University
Boston, MA, US

Sharon L. Hillier, PhD
Magee-Womens Hospital of UPMC
University of Pittsburgh
Pittsburgh, PA, US

James A. Hoxie, MD
University of Pennsylvania
Philadelphia, PA, US

Peter W. Hunt, MD
University of California San Francisco
San Francisco, CA, US

Harold W. Jaffe, MD
Centers for Disease Control and Prevention
Atlanta, GA, US

Ilesh V. Jani, MD, PhD
Instituto Nacional de Saúde
Maputo, Mozambique

Frank Kirchhoff, PhD
Institute of Molecular Virology
Ulm, Germany

Dennis L. Kolson, MD, PhD
University of Pennsylvania
Philadelphia, PA, US

Richard A. Koup, MD
Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health
Bethesda, MD, US

Hermione Lyall, MD
Imperial College Healthcare National Health Service Trust
London, England

James A. McIntyre, MBChB, FRCOG
Anova Health Institute
Johannesburg, South Africa

John W. Mellors, MD
University of Pittsburgh
Pittsburgh, PA, US

Ronald T. Mitsuyasu, MD
University of California Los Angeles
Los Angeles, CA, US

Andrew N. Phillips, PhD
University College London
London, England

Peter Reiss, MD, PhD
University of Amsterdam
Amsterdam, Netherlands

Douglas D. Richman, MD
University of California San Diego
La Jolla, CA, US

Jürgen K. Rockstroh, MD
University of Bonn
Bonn, Germany

Robert T. Schooley, MD
University of California San Diego
La Jolla, CA, US

Guido Silvestri, MD
Emory University and Yerkes National Primate Research Center
Atlanta, GA, US

Papa Salif Sow, MD, MSc
Bill and Melinda Gates Foundation
Seattle, WA, US
University of Dakar
Dakar, Senegal

Mario Stevenson, PhD
University of Miami
Miami, FL, US

Amalio Telenti, MD, PhD
The J. Craig Venter Institute
La Jolla, CA, US

David L. Thomas, MD
The Johns Hopkins University
Baltimore, MD, US

Alexandra Trkola, PhD
University of Zurich
Zurich, Switzerland

Community Liaison Subcommittee

The Community Liaison Subcommittee is a group of community educators and advocates that provides feedback to the PC about the content and structure of the scientific program in general and specifically related to scientific topics of interest to the HIV/AIDS-affected community.

Heidi M. Nass, JD
AIDS Treatment Activists Coalition
Madison, WI, US

Jeff Taylor
AIDS Treatment Activists Coalition
Palm Springs, CA, US

Morenike Ukpong, FWACS, MBA, BChD
Obafemi Awolowo University
Ife-Ife, Nigeria

Steven F. Wakefield
HIV Vaccine Trials Network
Fred Hutchinson Cancer Research Center
Seattle, WA, US

EXTERNAL REVIEWERS

We gratefully acknowledge the contributions of the following, who served as volunteer external reviewers of abstracts for CROI 2015.

Edward P. Acosta, PharmD
University of Alabama at Birmingham
Birmingham, AL, US

Peter L. Anderson, PharmD
University of Colorado
Aurora, CO, US

Till Bärnighausen, MD, PhD, ScD, MSc
Harvard University
Boston, MA, US

John M. Blandford, PhD
Centers for Disease Control and Prevention
Atlanta, GA, US

Marta Boffito, MD, PhD
Chelsea and Westminster Hospital and National Health Service Foundation Trust
London, United Kingdom

William Borkowsky, MD
New York University School of Medicine
New York, NY, US

Corey Casper, MD
Fred Hutchinson Cancer Research Center
Seattle, WA, US

Nicolas Chomont, PhD
Vaccine and Gene Therapy Institute of Florida
Port St Lucie, FL, US

David B. Clifford, MD
Washington University School of Medicine
Saint Louis, MO, US

Susan E. Cohn, MD
Northwestern University
Chicago, IL, US

Eric S. Daar, MD
Harbor–University of California Los Angeles Medical Center
Torrance, CA, US

Charles W. Flexner, MD
The Johns Hopkins University
Baltimore, MD, US

Patricia M. Flynn, MD
St. Jude Children's Research Hospital
Memphis, TN, US

Monica Gandhi, MD, MPH
University of California San Francisco
San Francisco, CA, US

J. Gerardo Garcia-Lerma, PhD
Centers for Disease Control and Prevention
Atlanta, GA, US

Carlo Giaquinto, MD
University of Padova
Padova, Italy

Francisco Gonzalez-Scarano, MD
University of Texas
San Antonio, TX, US

Steven K. Grinspoon, MD
Massachusetts General Hospital and Harvard University
Boston, MA, US

Huldrych F. Gunthard, MD
University Hospital Zurich
Zurich, Switzerland

Beatrice H. Hahn, MD
University of Pennsylvania
Philadelphia, PA, US

James G. Hakim, MD
University of Zimbabwe
Harare, Zimbabwe

Timothy B. Hallett, PhD
Imperial College London
London, United Kingdom

P. Richard Harrigan, MD
British Columbia Centre for Excellence in HIV/AIDS
Vancouver, BC, Canada

Diane V. Havlir, MD
University of California San Francisco
San Francisco, CA, US

Priscilla Y. Hsue, MD
University of California San Francisco
San Francisco, CA, US

Susan E. Krown, MD
AIDS Malignancy Consortium
New York, NY, US

Scott L. Letendre, MD
University of California San Diego
San Diego, CA, US

Sharon R. Lewin, MD
The Doherty Institute for Infection and Immunity
Melbourne, Australia

Susanna Naggie, MD, MHS
Duke Clinical Research Institute
Durham, NC, US

Jean-Michel Pawlotsky, MD, PhD
Henri Mondor University Hospital
Creteil, France

Sharon A. Riddler, MD
University of Pittsburgh
Pittsburgh, PA, US

Kenneth E. Sherman, MD
University of Cincinnati
Cincinnati, OH, US

Serena S. Spudich, MD, MA
Yale University
Guilford, CT, US

David L. Wyles, MD
University of California San Diego
San Diego, CA, US

Robert Yarchoan, MD
National Cancer Institute
Bethesda, MD, US

COMMERCIAL SUPPORT

The Conference on Retroviruses and Opportunistic Infections (CROI) is largely supported by the registration fees of participants. In addition, the organizers seek grants from commercial companies, particularly from companies with competing products. These companies have no input in or control over the selection of faculty or content of the presentations.

CROI 2015 has, to date, received grant support commitments from the following commercial companies:

Platinum

Gilead Sciences, Inc

Merck & Co, Inc

ViiV Healthcare

Gold

Bristol-Myers Squibb

Janssen Therapeutics, Division of Janssen Products, LP

Silver

AbbVie

Additional support has been provided by Mylan, Inc

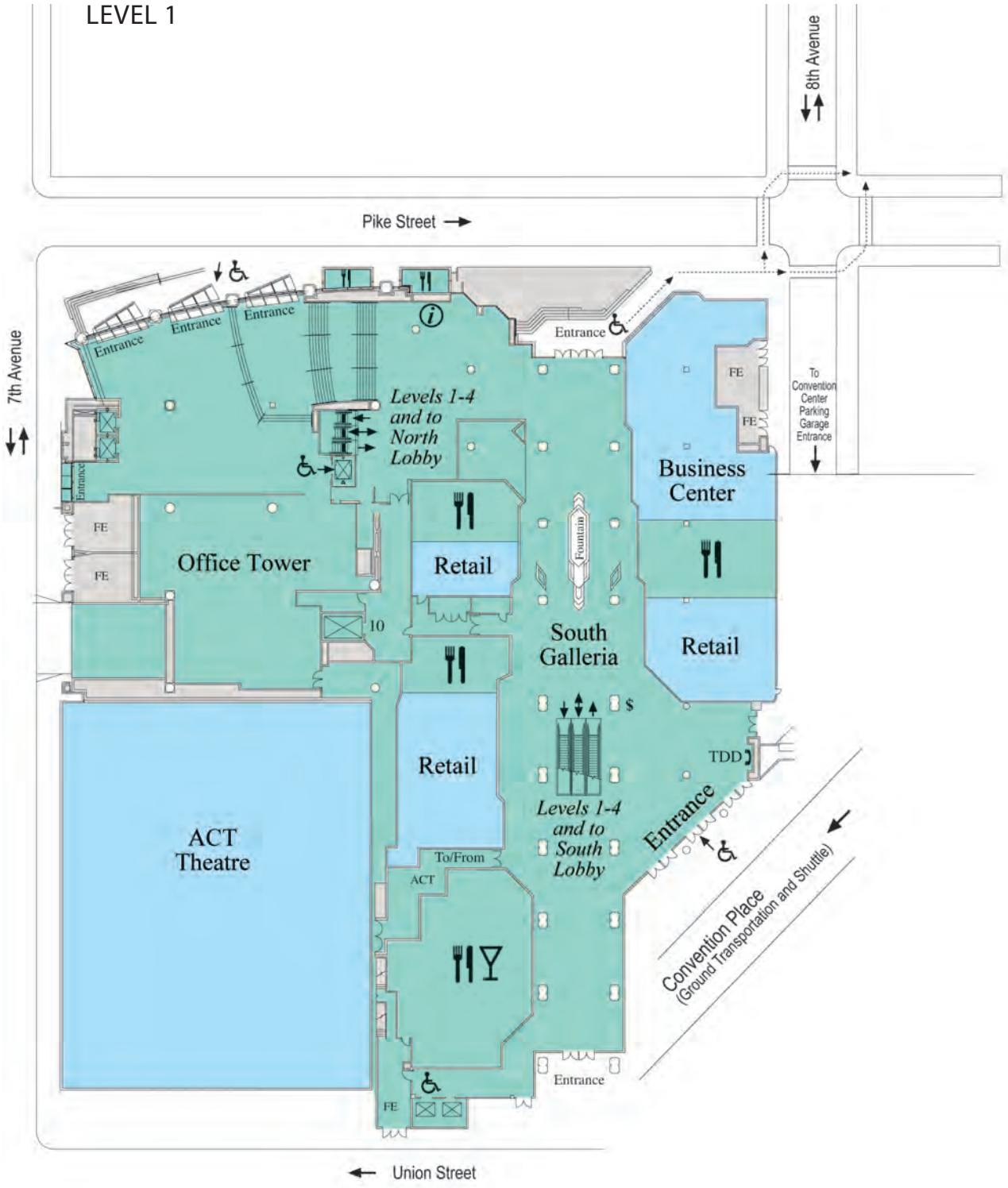
CONFERENCE SCHEDULE OVERVIEW

	Monday, February 23, 2015	Tuesday, February 24, 2015	Wednesday, February 25, 2015	Thursday, February 26, 2015
8:30 AM		**Plenary:** PrEP for HIV Prevention: What We Know and What We Need to Know for Implementation ***4AB Auditorium***	**Plenary:** Preventing Pediatric HIV and Managing HIV-Infected Children: Where Are We Now and Where Are We Going? ***4AB Auditorium***	**Plenary:** Cardiovascular Disease in HIV Patients: An Emerging Paradigm and Call to Action ***4AB Auditorium***
9:00 AM	**Workshop for New Investigators and Trainees** 9:00 AM to 12:30 PM ***Room 6E***	**Plenary:** Specific HIV Integration Sites Linked to Clonal Expansion and Persistence of Cells ***4AB Auditorium***	**Plenary:** Directing Chronic Virus Infection Through Viral Regulation of Innate Immune Defenses ***4AB Auditorium***	**Plenary:** The Price of Selling Sex: HIV Among Female Sex Workers—The Context and the Public Health Response ***4AB Auditorium***
9:30 AM				
10:00 AM		**ORAL ABSTRACT CONCURRENT SESSIONS** 10:00 AM to 12:15 PM **O-1:** Preventing HIV and HSV-2: What Will It Take? ***Room 6AB*** **O-2:** Prevention, Diagnosis, and Treatment of Pediatric HIV Infection ***Room 613*** **O-3:** Cellular Dynamics, Sensing, and Viral Restriction ***Room 615*** **O-4:** New Discoveries in HIV Pathogenesis ***Room 6D***	**ORAL ABSTRACT CONCURRENT SESSIONS** 10:00 AM to 12:15 PM **O-6:** Intracellular and Clinical Pharmacology, Drug Interactions, and Adherence ***Room 615*** **O-7:** KS and Cervical/Anal Dysplasia: Tale of 2 Tumors and TB and Other OIs ***Room 613*** **O-8:** Factors Affecting HIV Care and Outcome: Global Perspective ***Room 6E*** **O-9:** New Insights Into HIV Persistence, Latency Reversal, and Viremia Rebound ***Room 6D***	**ORAL ABSTRACT CONCURRENT SESSIONS** 10:00 AM to 12:15 PM **O-11:** Cardiovascular, Bone, and Kidney Health ***Room 6C*** **O-12:** Curing HCV: Mission Accomplished ***Room 6AB*** **O-13:** Reaching Populations: Demonstrating Impact ***Room 6D*** **O-14:** Immune Mechanisms: The Road to Protection ***Room 613***
12:15 PM		**LUNCH** 12:15 PM to 1:30 PM	**LUNCH** 12:15 PM to 1:30 PM	**LUNCH** 12:15 PM to 1:30 PM
12:30 PM	**LUNCH** 12:30 PM to 1:00 PM			
1:00 PM	**Martin Delaney Presentation** 1:00 PM to 2:00 PM **How to End the HIV Epidemic: Community Perspectives** ***Room 6E***			
1:30 PM		**THEMED DISCUSSION CONCURRENT SESSIONS** 1:30 PM to 2:30 PM **TD-B:** Next Generation of Next-Generation Sequencing ***Room 615*** **TD-C:** HIV/CMV Interactions in Transmission and Pathogenesis ***Room 613*** **TD-F:** Leaky Latency ***Room 6D*** **TD-Q:** Fat Without Borders: Metabolic Complications in Resource-Limited Settings ***Room 6AB*** **TD-S:** Hormonal Contraceptives: Enduring Controversy ***Room 6C*** **TD-Y:** Circumcision: Evolving Knowledge and Practice ***Room 6E***	**THEMED DISCUSSION CONCURRENT SESSIONS** 1:30 PM to 2:30 PM **TD-A:** Interferon: Triggers and Effectors ***Room 615*** **TD-H:** New Technologies in Assessing Drug Interactions and Systemic and Intracellular Pharmacology ***Room 613*** **TD-O:** Cancers in Young and Old, and Lung Cancer in HIV ***Room 6D*** **TD-R:** Cryptococcal Meningitis: Host Response, Treatment, and Outcomes ***Room 6E*** **TD-W:** Serosorting and Seroadaptive Behavior: What's Your Position? ***Room 6AB*** **TD-Z:** Economic Implications of ART ***Room 6C***	**THEMED DISCUSSION CONCURRENT SESSIONS** 1:30 PM to 2:30 PM **TD-M:** Identifying Recent Infections: Issues of False Recency ***Room 615*** **TD-N:** Next-Generation HCV Therapeutics: From Clinical Trials to the Clinic ***Room 6AB*** **TD-P:** Cardiovascular Risk Prediction: Can We Do Better? ***Room 6E*** **TD-T:** Keys to the Kingdom: Viral Suppression in Pregnant and Postpartum Women ***Room 6D*** **TD-V:** PEP: Remember Me? ***Room 6C***
2:00 PM				

2:30 PM	**CONCURRENT WORKSHOPS** 2:30 PM to 4:30 PM Clinical Trial Design and Analysis ***Room 6E*** Frontiers in Laboratory Science ***Room 6D*** Hepatitis C Care in the Interferon-Free Era ***Room 613***	**POSTER SESSIONS** 2:30 PM to 4:00 PM ***Poster Hall***	**POSTER SESSIONS** 2:30 PM to 4:00 PM ***Poster Hall***	**POSTER SESSIONS** 2:30 PM to 4:00 PM ***Poster Hall***
4:00 PM		**CONCURRENT SYMPOSIA** 4:00 PM to 6:00 PM **S-1:** Harnessing Antibodies for Prevention and Therapeutics ***Room 6C*** **S-2:** Current Issues in HIV-Related Malignancies ***Room 6D*** **S-3:** Current Imperatives in HIV Prevention and Treatment ***Room 6AB***	**CONCURRENT SYMPOSIA** 4:00 PM to 6:00 PM **S-4:** Making Sense of Sensing: Innate Immunity and HIV Infection ***Room 613*** **S-5:** Advancing HIV Prevention: Lessons From Biology, Medicine, and Public Health Law ***Room 6D*** **S-6:** Tuberculosis: Magic Bullets and Moving Targets ***Room 6E***	**CONCURRENT SYMPOSIA** 4:00 PM to 6:00 PM **S-7:** From Pathways to Paradigms: Applications of Systems Biology to HIV/Host Interactions ***Room 613*** **S-8:** Scale-Up of Interventions ***Room 6D*** **S-9:** HCV: New Frontiers and Controversies ***Room 6E***
4:30 PM				
5:00 PM	**Opening Session** 5:00 PM to 7:00 PM **Bernard Fields Lecture:** Hepatitis C: Light at the End of the Tunnel **N'Galy-Mann Lecture:** Antiretroviral Therapy: Past, Present, and Future ***4AB Auditorium***	**ORAL ABSTRACT SESSION** **O-5:** NeuroAIDS Pathogenesis and Antiretroviral Therapy ***Room 613***	**ORAL ABSTRACT SESSION** **O-10:** New Antiretroviral Agents, Strategies, and HIV Drug Resistance ***Room 6C***	
6:00 PM				
6:30 PM		**SPECIAL SESSION** 6:30 PM to 7:30 PM Ebola Virus Disease: Responding to the Challenge ***Room 6E***		
7:00 PM	**Welcome Reception** Nordstrom Downtown Seattle 500 Pine Street (Cross street 5th Ave) Seattle, WA 98101			

CONVENTION CENTER FLOOR PLANS

LEVEL 1



LEVEL 4

WSCC Use
Deli
M
W
North Service Corridor
Deli
North Loading Dock
Poster Hall 4EF
To/From The Conference Center
Cyber Cafe 4D
Pike Street (Below)
Truck Bridge
South Service Corridor
Deli
Open
To/From Level 3
North Lobby
400
Registration 4C
4AB
South Loading Dock
Truck Ramp To Hubbell Place
WSCC Use
416
401
454
439
438
To/From Level 6
South Galleria
South Lobby
To/From Levels 5 & 6
Waterfall Suite
Ellis Plaza

LEVEL 6

FE
Service
FE
Service
FE
Service
FE
Service
FE
FE
6E
6C
6AB
10
618
619
620
(6F)
615
M
W
613
6D
W
M
604
603
602
FE
657
Suite C
Suite A
West Lobby
To/From Level 4
FE
M
W
FE
East Lobby
601
Terrace
FE
To/From Level 4
To/From Levels 4 & 5
South Galleria (Below)
South Lobby (Below)

CONTINUING MEDICAL EDUCATION

Accreditation Statement

The International Antiviral Society–USA (IAS–USA) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education (CME) for physicians.

The IAS–USA designates this live activity for a maximum of **28 AMA PRA Category 1 Credits™**. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Since 2006, the IAS–USA has held Accreditation with Commendation. In so doing, the IAS–USA belongs to an elite group of organizations in the United States that have been awarded this prestigious status, which, in the words of the ACCME, is "reserved for programs that are truly exceptional."

Objectives

After participating in CROI 2015, learners will be able to:

- Describe current basic science research on the pathogenesis of HIV and on advances toward a cure
- Discuss the most recent findings from clinical trials in the field of HIV and the implications of these data for state-of-the-art treatment strategies
- Review current epidemiologic data on the prevalence of HIV infection, transmission, treatment, and linkage to and retention in care in populations worldwide, and discuss the implications of these data for public-health program planning

Statement of Need

Since HIV was identified, the scientific response to the global pandemic has been a coordinated effort among basic researchers, clinical investigators, health care providers, epidemiologists, and community leaders to move information and potential treatment options from research to clinical trials and out to affected communities as quickly as possible. CROI was founded in 1993 by researchers working in the field of HIV/AIDS and its complications, as a science-focused forum for exchanging current research findings among their international peers. CROI continues to focus on scientific exchange, providing an environment in which basic science researchers, translational researchers, clinical investigators, epidemiologists, and public health experts meet to present and discuss the latest research into different facets of HIV and its complications.

CME Credit Information

Physicians (MD, DO, and international equivalents) are eligible to receive CME credit for participation in CROI 2015. Other practitioners and clinicians can receive a Certificate of Participation verifying their attendance, as required by the American Medical Association (AMA).

Claiming CME Credits or a Certificate of Participation

During the conference, daily evaluations will be e-mailed to all CROI participants to the e-mail account they used to register for the conference. On Thursday, February 26, 2015, all CROI participants will receive a final e-mail that will contain their registration confirmation number and a link to the overall CROI evaluation. To obtain CME credits or a Certificate of Participation for CROI, this final evaluation must be completed by Tuesday, March 31, 2015. Once the evaluation is submitted, participants will receive the link to claim and print their certificate.

To determine the number of CME credits or hours that you can claim, calculate your time spent attending the conference, including plenary sessions, symposia, themed discussions, etc. For example, if you attended 2 plenary talks (8:30 AM to 9:30 AM), a themed discussion (1:30 PM to 2:30 PM), and a symposium (4:00 PM to 6:00 PM), you would have a total of 4 hours to apply toward CME credits for that day. At the end of CROI, please add the total hours you attended for your certificate. You may claim a maximum of **28 AMA PRA Category 1 Credits™** for this activity.

A CME hour worksheet can be found here: http://www.croiconference.org/sites/default/files/uploads/croi2015_cme_worksheet.pdf.

Faculty Financial Disclosure

It is the policy of the IAS–USA to ensure balance, independence, objectivity, and scientific rigor in all its educational activities. All faculty members (speakers, presenters, etc) participating in IAS–USA-sponsored activities are required to disclose to the program audience any financial interests within the past 12 months that could be perceived to influence, or give the appearance of potentially influencing, the written or oral presentation. (The ACCME defines a financial interest as an interest in any amount.) The information is intended to make the IAS–USA audience aware of author and contributor interests and commitments with commercial companies or other entities, enabling the audience members to form their own judgments about such associations.

Each author or contributor is required to complete this financial disclosure declaration. In accordance with IAS–USA policy, the IAS–USA will identify and resolve ahead of time any possible conflicts of interest that may influence CME activities with regard to exposition or conclusion. Disclosure information will be included with the Program and Abstracts eBook on the web.

Drug and Product Disclaimer

This activity may contain information about the investigational uses of drugs or products that are not approved by the US Food and Drug Administration. Please consult full prescribing information before using any medication or product mentioned in this activity.

GENERAL INFORMATION

Overview

The 2015 Conference on Retroviruses and Opportunistic Infections (CROI) will take place at the Washington State Convention Center in Seattle, WA, from February 23 to February 26, 2015. CROI was established in 1993 to provide a forum for basic scientists and clinical investigators to present, discuss, and critique their investigations into the epidemiology and biology of human retroviruses and associated diseases. The synergy of basic science and clinical investigation has been a major contributor to the success of the meeting. CROI is the preeminent HIV research meeting in the world and attracts more than 4000 HIV and AIDS research leaders internationally. The goal of the conference is to help researchers translate their laboratory and clinical findings into tangible progress against the HIV pandemic. CROI has facilitated the presentation of important discoveries in the field, thereby accelerating progress in HIV and AIDS research.

Americans with Disabilities Act

CROI 2015 endeavors to comply fully with the legal requirements of the Americans with Disabilities Act (ADA). If you require assistance on-site, please visit the Seattle Visitor Center and Concierge Services in the Upper Pike Street Lobby during the conference.

Ebola Precautions

Attendees who have recently returned from an Ebola-prevalent area are expected to follow the guidance of their institutions, local health departments, or the Centers for Disease Control and Prevention (CDC) as applicable with respect to monitoring and travel. CDC guidance can be found online: http://www.cdc.gov/vhf/ebola/exposure/monitoring-and-movement-of-persons-with-exposure.html.

Welcome Reception

All registered CROI attendees are invited to join us for a Welcome Reception immediately following the Opening Reception on February 23, 2015. This will be a private event hosted at Nordstrom's Flagship store in Downtown Seattle just a minutes walk from the Convention Center at Sixth and Pine Streets (enter using the Sixth Avenue entrance).

This unique Welcome Reception will offer attendees the opportunity to network with colleagues and experience a private shopping environment while enjoying passed hors d'oeuvres and beverages in a beautiful and unique setting.

Please join us for this exclusive event!

Meals

Morning coffee and light continental breakfast will be available to conference registrants from 9:30 AM to 10:00 AM, Tuesday, Wednesday, and Thursday, on the 6th floor. An afternoon snack break will be available at 2:30 PM in the Poster Hall and before the special session on Tuesday evening. Attendees are on their own for lunch each day. Below is a list of food service options located in the Convention Center or within a short walking distance.

At the Convention Center

820 Pike Street – Pan Asian Cuisine
Crêpes Voilá
Cyber Dogs – Internet Café
Espresso Caffé Dior
Goldberg's Deli
Subway Sandwiches
Taco Del Mar
The Juicy Café
Tully's Coffee
Wild Rye Café Bakery

Within 4 Blocks of the Convention Center

Benihana
Blueacre Seafood
Blue C Sushi
Daily Grill
Dragonfish Asian Cafe
FareStart
FOX Sports Grill
Gameworks
Gordon Biersch Brewery Restaurant
Il Fornaio
MOD Superfast Pizza
Morton's The Steakhouse
Ebar (Nordstrom Downtown Seattle)
Marketplace Café (Nordstrom Downtown Seattle)
The Grill (Nordstrom Downtown Seattle)
NYC Hyatt Deli Market
P.F. Chang's China Bistro – Seattle
Palomino
Pike Place Chowder – Pacific Place
Potbelly Sandwich Shop
RN74
Rock Bottom Restaurant & Brewery
Ruth's Chris Steak House
Soup's On!
Starbucks Coffee Company
Sullivan's Steakhouse
Tango Restaurant & Lounge
Tap House Grill
Thai Ginger
The Capital Grille
The Cheesecake Factory
The Elephant and Castle Pub & Restaurant
Toss'd Custom Salads
Urbane Northwest (Hyatt at Olive 8)

Overflow Accommodations for Session Rooms

The 4AB Auditorium is the designated overflow area. Headsets and up to 4 screens will provide live audio and video feed throughout the conference.

USB Flash Drive

Each participant is supplied a USB flash drive at badge pickup with a copy of the eAbstract book. The Program at a Glance and Program and Abstracts eBook are also available online to be loaded onto the USB flash drive. Downloads can be completed at the Cyber Cafe or directly from the conference website.

Website

For additional information about the conference please visit the website at www.CROIconference.org.

Webcasts and Podcasts

Plenaries, symposia, scientific overviews, oral abstract sessions, and themed discussions will be webcast and podcast. Webcasts are also available as streaming video for the Apple iPad and iPhone.

Visit www.CROIconference.org or www.CROIwebcasts.org to access the CROI 2015 webcasts and podcasts. Webcasts will be available within 24 hours of the end of the relevant session.

Mobile App

CROI 2015 has a mobile App to enhance your conference experience. The App enables you to schedule sessions, view abstracts, e-mail session notes, receive announcements, and more. Search "CROI 2015" in your mobile device App store, and download the conference App. The mobile App supports iOS and Android devices. Access is restricted to registered attendees only. Your log-in information and password will be provided to you on site with your registration materials.

Wi-Fi Access at the Conference

Complimentary Wi-Fi access is provided at the Washington State Convention Center. Network information is as follows:

Network name: CROI 2015

Password: iasusa2015

Badges

Badge pickup will be available at the registration lobby; please bring government-issued photo identification that clearly shows your name. You must wear your name badge to gain entry to all official meeting activities, including the poster sessions. **DO NOT LOSE YOUR BADGE. Unfortunately, payment of an additional registration fee ($730) will be required to replace a lost badge.** Also, if you notice that your affiliation or the affiliations of other attendees are incorrect, please inform conference staff in the office of the Conference Secretariat.

Child Care

Children are not permitted entry into any meeting room, including the poster area. If you should require child care, please contact the concierge of your hotel or the Visitor Information Center on Level One at the Washington State Convention Center.

Conference Etiquette

Please ensure all cell phones and pagers are off or are placed in SILENT mode. No flash photography is permitted in session rooms.

CONFERENCE SERVICES AT THE WASHINGTON STATE CONVENTION CENTER

Services	Location	Hours	Notes
Seattle Visitor Center and Concierge Services	Upper Pike Street Lobby Level 1	Monday to Friday 9:00 AM–5:00 PM	Full-service concierge assistance, including maps, guides, tickets, restaurant reservations, tours, ground transportation, and personal services
Bag and Coat Check	Hall 4C-3, 4 Level 4	Monday 7:00 AM–7:30 PM, Tuesday 7:00 AM–8:00 PM, Wednesday to Thursday 7:30 AM–6:30 PM	Bag and coat check are free of charge.
Cyber Cafe	4D Skybridge Level 4	Sunday 3:00 PM–5:00 PM, Monday to Wednesday 7:00 AM–7:00 PM, Thursday 7:00 AM–6:00 PM	Computers with Internet access available for webcasts, abstract searches, and messages
Media Center	Room 400 Level 4	Monday 9:00 AM–7:00 PM, Tuesday to Thursday 8:00 AM–6:30 PM	There is no on-site press registration. Registered press can pick up press kits and obtain location for press conferences.
Badge Pickup Attendee Services Housing Information Scholarship Badge Pickup Media Badge Pickup	Hall 4C-3,4 Level 4	Sunday 3:00 PM–6:00 PM, Monday 7:00 AM–7:00 PM, Tuesday 7:00 AM–6:00 PM, Wednesday 8:00 AM–6:00 PM, Thursday 8:00 AM–12:00 PM	Location to pick up badges and conference materials
Speaker Ready Room and Electronic Poster Drop-off	Room 620 Level 6	Sunday 3:00 PM–6:00 PM, Monday to Thursday 7:30 AM–6:00 PM	Oral abstract, invited, and themed discussion session speakers must drop off presentations at least 24 hours before their presentation. **Poster presenters must submit an electronic version of their poster for placement on the CROI website before their assigned session.**
Personal Considerations Room	Room 507 Level 5	Sunday 3:00 PM–6:00 PM, Monday 7:00 AM–7:00 PM, Tuesday 7:00 AM–6:00 PM, Wednesday 8:00 AM–6:00 PM, Thursday 7:00 AM–6:00 PM	The Personal Considerations Room is a room set aside for those who require a short-term private space for personal health needs. Use of this room is on a first-come, first-served basis.
New Mother's Room	Room 416 Level 4	Sunday 3:00 PM–6:00 PM, Monday 7:00 AM–7:00 PM, Tuesday 7:00 AM–6:00 PM, Wednesday 8:00 AM–6:00 PM, Thursday 7:00 AM–6:00 PM	The New Mother's Room is a room set aside for nursing mothers who require a short-term private room. Use of this room is on a first-come, first-served basis.

HOTEL INFORMATION

CROI 2015 hotels are listed below. For more detailed housing information, please visit the CROI 2015 conference website: www.CROI2015.org/housing. Conference attendees are required to stay in one of the official conference hotels. The few exceptions to this include registrants who live in the Seattle area (ie, within a 50-mile radius of the Washington State Convention Center) and registrants who are sharing a room with an approved CROI attendee with accommodations booked via the CROI housing system.

Sheraton Seattle Hotel
1400 Sixth Avenue
Seattle, WA 98101
PH: +1 206 621 9000

Crowne Plaza Seattle Downtown
1113 6th Avenue
Seattle, WA 98101
PH: +1 206 464 1980

The Fairmont Olympic Hotel
411 University Street
Seattle, WA 98101
PH: +1 206 621 1700

Hilton Seattle
1301 6th Avenue S
Seattle, WA 98101
PH: +1 206 460 7456

Grand Hyatt Seattle
721 Pine Street
Seattle, WA 98101
PH: +1 206 774 1234

Hyatt at Olive 8
1635 8th Avenue
Seattle, WA 98101
PH: +1 206 695 1234

Mayflower Park Hotel
405 Olive Way
Seattle, WA 98101
PH: +1 206 623 8700

Motif Seattle
1415 Fifth Avenue
Seattle, WA 98101
PH: +1 206 971 8000

Renaissance Seattle Hotel
515 Madison Street
Seattle, WA 98104
PH: +1 206 583 0300

W Seattle
1112 4th Avenue
Seattle, WA 98101
PH: +1 206 264 6000

The Westin Seattle
1900 5th Avenue
Seattle, WA 98101
PH: +1 206 728 1000

CROI 2015
February 23 – 26, 2015
CROI 2015 SEATTLE
IAS-USA International Antiviral Society-USA
SEATTLE CENTER
CHIHULY GARDEN & GLASS
PACIFIC SCIENCE CENTER
EMP MUSEUM
BILL & MELINDA GATES FOUNDATION
LAKE UNION PARK
MOHAI
DENNY PARK
MYRTLE EDWARDS PARK
OLYMPIC SCULPTURE PARK
Ferry to Victoria B.C.
PIER 69
VICTORIA CLIPPER
PIER 67
BELL HARBOR CONFERENCE CENTER
PIERS 62 & 63
PIER 59
SEATTLE AQUARIUM
WATERFRONT PARK
PIER 57
SEATTLE GREAT WHEEL
PIER 55
ARGOSY CRUISES/TILLICUM VILLAGE
Ferry to Tillicum Village
STEINBRUECK PARK
PIKE PLACE MARKET
WESTLAKE PARK
WASHINGTON STATE CONVENTION CENTER
PIER 52
WA STATE FERRIES
PIONEER SQUARE
CHINATOWN/ INT'L DISTRICT
CENTURYLINK FIELD
CENTURYLINK EVENT CENTER
SAFECO FIELD
DR. JOSE RIZAL PARK
N
S
E
W
CROI HOTELS
1. Sheraton Seattle Hotel
2. Crowne Plaza Hotel Seattle
3. The Fairmont Olympic Hotel
4. Grand Hyatt Seattle
5. Hilton Seattle
6. Hyatt at Olive 8
7. Mayflower Park Hotel
8. Motif Seattle
9. Renaissance Seattle Hotel
10. W Seattle
11. The Westin Seattle
WELCOME RECEPTION VENUE
12. Nordstrom Downtown Seattle
VISIT seattle
Pike Place Market to Convention Center: ½ mi / 800 m
MAJOR ATTRACTION
PARK
BUS/LIGHT RAIL TUNNEL STATION
CROI HOTELS
S. LAKE UNION STREETCAR
BUS/LIGHT RAIL TUNNEL
SEATTLE CENTER MONORAIL
INFORMATION CENTER

ABSTRACTS

Scientific Categories

A Virology
B Molecular Epidemiology and HIV/SIV Evolution
C Pathogenesis: Human Studies and Animal Models
(D Pathogenesis: Animal Models has been combined with category C)
E Host Immune Responses to Infection, Vaccines, and Immunotherapy
F HIV Persistence, Reservoirs, Latency, Eradication, Including Gene Therapy
G Neuropathogenesis
H Clinical Pharmacology
I Antiretroviral Therapy: Preclinical Studies
J Antiretroviral Therapy: Randomized Clinical Trials
K Antiretroviral Therapy: Observational Studies
L HIV Drug Resistance
M HIV Diagnostics
N Hepatitis Viruses
O HIV-Related and Non–HIV-Related Malignancies
P Cardiovascular Complications of HIV
Q Other Complications of HIV Infection and Antiretroviral therapy
R Tuberculosis and Other Opportunistic Infections
S HIV in Women and Women's Health
T Maternal/Fetal HIV
U Pediatrics and Adolescents
V Prevention and Intervention Studies
W Epidemiology
X Health Care Delivery and Health Systems
Y Implementation Science
Z Population and Economic Modeling

Abstract Content

Author names, institutions, abstract titles, and abstracts in the Program and Abstracts eBook are generally presented as submitted by the corresponding author.

Abstract Review Process

The PC and a panel of external reviewers reviewed the more than 1900 submitted abstracts. Each abstract was scored by 5 to 10 reviewers selected for each abstract category based upon their individual expertise.

PC members and external experts in the field reviewed the abstracts for the quality and originality of the work and scored them numerically. All reviewers were instructed to abstain from scoring any abstract on which they are an author or coauthor, have a financial or personal conflict of interest, or do not have the appropriate expertise to evaluate.

Scores for each abstract were averaged and the standard deviation was calculated to assess variability. If variability was high, outlier scores are identified and censored. Abstracts with high variability in scores were discussed individually during a series of conference calls.

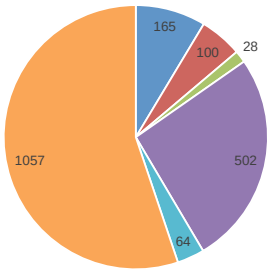
Common Reasons for Abstract Rejection

- Information is not new enough
- Methodology is inadequate or insufficient to support conclusions
- Background does not summarize the hypothesis; submission is poorly written
- Abstract is duplicative of other submissions
- Abstract is not appropriate for CROI
- Controls are absent or inadequate
- Statistical evaluation is inadequate or absent
- Summary of essential results is inadequate or absent
- Data are inadequate or insufficient to support conclusions
- Submission reports clinical trial and data from unplanned analysis or incomplete or ongoing studies
- Format does not follow guidelines (eg, section[s] missing, more than 1 graphic, table, or figure submitted)

Statistics

Abstracts

Total general abstracts submitted:	1921
Total general abstracts accepted:	1016
General oral abstracts:	95
General poster abstracts:	921
Total late-breaker abstracts submitted:	195
Total late-breaker accepted:	43
Late-breaker oral abstracts:	24
Late-breaker poster abstracts:	19
Total abstracts submitted:	2116
Total abstracts accepted:	1059



Submitted Abstracts

Africa	165	9%
Asia	100	5%
Australia	28	1%
Europe	502	26%
Latin & South America	64	3%
North America	1057	55%

EMBARGO POLICY

General

The research presented at CROI 2015 is embargoed until the conclusion of the session in which it is presented. For example, if a study is presented from 2:15 PM to 2:30 PM as part of a session that ends at 3:00 PM, the embargo on that study lifts at 3:00 PM. Embargoes on poster presentations lift at the conclusion of the session in which the poster is presented. If a study to be presented at CROI 2015 is included in an official CROI press conference and that press conference takes place before the official presentation of the study at the conference, the embargo lifts at the conclusion of the press conference in which that study is featured.

Social Media

CROI embargo policies apply to any public dissemination of research information presented at the conference, including through electronic publication (eg, blogs) or social media (eg, Facebook, Twitter). No public dissemination of research information from the conference is permitted prior to the lifting of the conference embargo.

Individuals or organizations that violate the conference embargo policy may have their conference credentials revoked and may forfeit the opportunity to participate in future conferences.

YOUNG INVESTIGATOR AWARDEES

Enass Abdel-Hameed
University of Cincinnati, Cincinnati, OH, US

Mohamed Abdel-Mohsen
Blood Systems Research Institute, San Francisco, CA, US

Joella Adams
AIDS Activities Coordinating Office, Philadelphia, PA, US

Fernando Agüero
Hospital Clinic, Barcelona, Spain

Erika Ahlgren
University of Gothenburg, Gothenburg, Sweden

Gerrit Ahrenstorf
Hannover Medical School, Hannover, Germany

Abhinav Ajaykumar
University of British Columbia, Vancouver, BC, Canada

Hisashi Akiyama
Boston University School of Medicine, Boston, MA, US

Muntasir Alam
Kumamoto University, Kumamoto, Japan

Selma Alva Hernández
Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico

Elizabeth Anderson
National Cancer Institute, Frederick, MD, US

Viviane Andrade
University of Miami, Miami, FL, US

Birgitta Anesten
Sahlgrenska Academy, Göteborg, Sweden

Sofia Appelberg
University of Florida, Gainesville, FL, US

Daniele Armenia
University of Rome Tor Vergata, Rome, Italy

Eugene Asahchop
University of Alberta, Edmonton, AB, Canada

Aditya Bade
University of Nebraska Medical Center, Omaha, NE, US

Joëlle Bader
University of Basel, Basel, Switzerland

Nathan Bahr
University of Minnesota, Minneapolis, MN, US

Laurie Baker
University of Missouri–St Louis, St Louis, MO, US

Ester Ballana
IrsiCaixa–AIDS Research Institute, Badalona, Spain

István Bartha
École Polytechnique Federale De Lausanne, Lausanne, Switzerland

Brian Basco
Washington University in St Louis School of Medicine, St Louis, MO, US

Matteo Basilissi
University of Milan, Milano, Italy

Ashita Batavia
Weill Cornell Medical College, New York, NY, US

Amy Baugher
Centers for Disease Control and Prevention, Atlanta, GA, US

Sanjiv Baxi
University of California San Francisco, San Francisco, CA, US

Maria Bednar
University of North Carolina at Chapel Hill, Durham, NC, US

Rachel Bender Ignacio
University of Washington, Seattle, WA, US

Kian Bichoupan
Icahn School of Medicine at Mount Sinai, New York, NY, US

Rimke Bijker
Amsterdam Institute of Global Health and Development, Amsterdam, Netherlands

Tamara Sonia Boender
Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands

Christoph Boesecke
Bonn University Hospital, Bonn, Germany

Álvaro Borges
Rigshospitalet, Copenhagen, Denmark

Joanna Bove
University of Washington, Seattle, WA, US

Anders Boyd
Inserm UMR S1136, Paris, France

Vedran Brezar
Inserm U955, University Paris Est Créteil, Vaccine Research Institute, Créteil, France

Egidio Brocca-Cofano
University of Pittsburgh, Pittsburgh, PA, US

Katherine Brooks
Brown University, Providence, RI, US

Matthew Buechler
University of Washington, Seattle, WA, US

Lisa Burch
University College London, London, UK

Helen Byakwaga
Mbarara University of Science and Technology, Mbarara, Uganda

Kieran Cashin
Burnet Institute, Melbourne, Australia

Jessica Castilho
Vanderbilt University Medical Center, Nashville, TN, US

Brian Chan
Brigham and Women's Hospital, Boston, MA, US

Iris Chen
Johns Hopkins School of Medicine, Baltimore, MD, US

Xinhui Chen
University of Colorado, Aurora, CO, US

Ankita Chowdhury
Emory University, Atlanta, GA, US

Anthony Cillo
University of Pittsburgh, Pittsburgh, PA, US

Meredith Clement
Duke University Medical Center, Durham, NC, US

Anna Coghill
National Cancer Institute, Rockville, MD, US

Sophie Cohen
Emma Children's Hospital of the Academic Medical Center, Amsterdam, Netherlands

Jonathan Colasanti
Emory University, Atlanta, GA, US

Anna Cope
University of North Carolina, Chapel Hill, NC, US

Jennifer Dan
University of California San Diego, La Jolla, CA, US

Prasanta Dash
University of Nebraska Medical Center, Omaha, NE, US

Giffin Daughtridge
University of Pennsylvania, Philadelphia, PA, US

Tyler Day
University of California San Diego, La Jolla, CA, US

Lesley de Armas
University of Miami, Miami, FL, US

Marieke de Pundert
Amsterdam Institute for Global Health and Development, Netherlands

David Del Bello
Mount Sinai Medical Center, New York, NY, US

Mark Dela Cruz
University of California San Francisco, San Francisco, CA, US

Heloise Delagreverie
Assistance Publique–Hôpitaux de Paris, Hôpital Saint Louis, Paris, France

Laura DeMaster
University of Pennsylvania, Philadelphia, PA, US

Gilad Doitsh
Gladstone Institute, San Francisco, CA, US

Natasha Durham
Icahn School of Medicine at Mount Sinai, New York, NY, US

Ramy El-Diwany
Johns Hopkins University School of Medicine, Baltimore, MD, US

Latesha Elopre
University of Alabama at Birmingham, Birmingham, AL, US

Nathaniel Erdmann
University of Alabama at Birmingham, Birmingham, AL, US

Daniel Escudero
Brown University, Providence, RI, US

Kimberly Faldetta
National Institutes of Health, Bethesda, MD, US

Michelli Faria de Oliveira
University of California San Diego, La Jolla, CA, US

Pariya Fazeli
University of California San Diego, La Jolla, CA, US

Anna Feldmann
Max Planck Institute for Informatics, Saarbrücken, Germany

Francesca Ferretti
San Raffaele Scientific Institute, Milan, Italy

Virginie Fievez
Centre Hospitalier de Luxembourg, Luxembourg

Erin Finn
University of Colorado Denver, Denver, CO, US

Brooke Fokker
Erasmus University Medical Center, Rotterdam, Netherlands

Oliver Fregoso
Fred Hutchinson Cancer Research Center, Seattle, WA, US

Riccardo Freguja
Paediatric European Network for Treatment of AIDS Foundation, Padova, Italy

Jennifer Fulcher
University of California Los Angeles, Los Angeles, CA, US

Mónica García-Álvarez
Instituto de Salud Carlos III, Madrid, Spain

Claudia Garcia-Morales
Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico

Carolina Garrido
University of North Carolina, Chapel Hill, NC, US

Esther Gathogo
King's College London, London, UK

Christina Gavegnano
Emory University, Atlanta Veterans Affairs Medical Center, Atlanta, GA, US

Ketty Gianesin
University of Padova, Padova, Italy

Alexander Gill
University of Pennsylvania, Philadelphia, PA, US

Shawn Gogia
University of California San Francisco, San Francisco, CA, US

Alejandro Gonzalez-Serna
British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

Shayarana Gooneratne
University of Melbourne, Melbourne, Australia

Mary Grabowski
Johns Hopkins University, Baltimore, MD, US

Nella Green
University of California San Diego, La Jolla, CA, US

Alberto Guardo
Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain

Yolanda Guillén
IrsiCaixa, Badalona, Spain

Dongwei Guo
University of Nebraska Medical Center, Omaha, NE, US

Andreas Haas
University of Bern, Bern, Switzerland

Lisa Hamzah
King's College London, London, UK

Yasmeen Hanifa
London School of Hygiene & Tropical Medicine, London, UK

Michael Harper
University of Colorado, Anschutz Medical Campus, Denver, CO, US

Said Hassounah
Lady Davis Institute, McGill University, Montréal, QC, Canada

Jason Hataye
National Institute of Allergy and Infectious Diseases, Bethesda, MD, US

Camilla Ingrid Hatleberg
Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Rulin Hechter
Kaiser Permanente Southern California, Pasadena, CA, US

Tiffany Hensley-McBain
University of Washington, Seattle, WA, US

Alfonso Hernandez-Romieu
Rollins School of Public Health, Emory University, Decatur, GA, US

Emma Hodcroft
University of Edinburgh, Edinburgh, UK

Martin Hoenigl
University of California San Diego, La Jolla, CA, US

Christian Hofmann
University of California Los Angeles, Los Angeles, CA, US

Marije Hofstra
University Medical Center Utrecht, Utrecht, Netherlands

Feiyu Hong
University of Pittsburgh, Pittsburgh, PA, US

Julia Hood
Public Health Seattle & King County, Seattle, WA, US

Nina Hosmane
Johns Hopkins University School of Medicine, Baltimore, MD, US

Malene Hove
Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Denise Hsu
National Institutes of Health, Bethesda, MD, US

Sebastiaan Hullegie
Erasmus University Medical Center, Rotterdam, Netherlands

Shilpa Iyer
University of Pennsylvania, Philadelphia, PA, US

Patrick Jackson
University of Virginia, Charlottesville, VA, US

Shameem Jaumdally
University of Cape Town, Cape Town, South Africa

Kara Jensen
University of North Carolina at Chapel Hill, Chapel Hill, NC, US

Leah Jimmerson
University of Colorado, Aurora, CO, US

Erica Johnson
Emory University School of Medicine, Atlanta, GA, US

Jeffrey Joy
British Columbia Centre for Excellence, Vancouver, BC, Canada

Dominik Kaczmarek
University of Bonn, Bonn, Germany

Philipp Kaiser
San Francisco Veterans Affairs Medical Center, San Francisco, CA, US

Aaron Karat
London School of Hygiene & Tropical Medicine, Barrow-in-Furness, UK

Sharon Karmon
Aaron Diamond AIDS Research Center, San Francisco, CA, US

Lilian Kebaya
University of Nairobi, Nairobi, Kenya

Julia Kenny
Institute of Child Health, University College London, London, UK

Palwasha Khan
London School of Hygiene & Tropical Medicine, Walsall, UK

Christine Khosropour
University of Washington, Seattle, WA, US

Georges Khoury
Peter Doherty Institute for Infection and Immunity, Melbourne, Australia

Zahra Kiani
McGill University, Montreal, QC, Canada

Jon Kibbie
University of Colorado Denver School of Medicine, Englewood, CO, US

Suzanne Kijewski
Boston University, Boston, MA, US

Connie Kim
Toronto General Hospital, Toronto, ON, Canada

Allison Kirkpatrick
National Institute of Allergy and Infectious Diseases, Baltimore, MD, US

Payal Kohli
University of California San Francisco, San Francisco, CA, US

Yik Lim Kok
University Hospital Zurich, Zurich, Switzerland

Pavlos Kokordelis
University of Bonn, Bonn, Germany

Katherine Kooij
Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands

Catherine Koss
University of California San Francisco, San Francisco, CA, US

Lenche Kostadinova
Case Western Reserve University, Cleveland, OH, US

Benjamin Krämer
University of Bonn, Bonn, Germany

Edward Kreider
University of Pennsylvania, Philadelphia, PA, US

Moussa Laanani
Inserm, Le Kremlin-Bicêtre, France

Nathan Lachowsky
British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada

Kathryn Lancaster
University of North Carolina at Chapel Hill, Chapel Hill, NC, US

Kamilla Laut
Centre for Health and Infectious Disease Research, Copenhagen, Denmark

Lorna Leal
Hospital Clínic of Barcelona, Barcelona, Spain

Frederick Lee
St Vincent's Hospital, Sydney, Australia

Wing-Yiu Jason Lee
Blizard Institute, Queen Mary University of London, London, UK

Ellen Leitman
University of Oxford, Oxford, UK

Yew Ann Leong
Monash University, Melbourne, Australia

Catherine Lesko
University of North Carolina at Chapel Hill, Chapel Hill, NC, US

Duo Li
University Hospital of Zurich, Zurich, Switzerland

Zhe Li
University of Missouri, Columbia, MO, US

Camille Libre
Institut de Biologie Moléculaire et Cellulaire, Strasbourg, France

Sophie Limou
National Cancer Institute, Frederick National Lab, Frederick, MD, US

Kuan-Hung Lin
University of Massachusetts Medical School, Worcester, MA, US

Nathan Lo
Stanford University School of Medicine, Stanford, CA, US

Claire Loiseau
Inserm 1043, Toulouse, France

Mark Lucera
Case Western Reserve University, Cleveland, OH, US

Louise Lundgren
Critical Care Medicine Department, National Institutes of Health, Copenhagen, Denmark

Victoria Lutgen
Rush University Medical Center, Chicago, IL, US

Alain Makinson
University Hospital, Montpellier, France

Tara Mangal
Imperial College London, London, UK

Lara Manganaro
Icahn School of Medicine at Mount Sinai, New York, NY, US

Jennifer Manuzak
Inserm U1016 - Institut Cochin, Paris, France

Letizia Marinaro
University of Torino, Turin, Italy

Jenniffer Maroa
KwaZulu-Natal Research Institute for Tuberculosis and HIV, Durban, South Africa

Philip Martin
University of Liverpool, Liverpool, UK

David Martinez
Duke University, Durham, NC, US

Enrique Martin-Gayo
Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard, Boston, MA, US

Alex Marzel
University Hospital Zurich, Zurich, Switzerland

Catia Marzolini
University Hospital Basel, Basel, Switzerland

Marta Massanella
University of California San Diego, La Jolla, CA, US

Jack Masur
Institute of Human Virology, University of Maryland, Baltimore, MD, US

Mark McGovern
Harvard University, Boston, MA, US

Luca Micci
Yerkes National Primate Research Center, Emory University, Atlanta, GA, US

Benedetta Milanini
Institute of Infectious Diseases, Catholic University, Rome, Italy

Caitlin Milligan
Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US

Michael Milligan
Harvard Medical School, Boston, MA, US

Gayatri Mirani
Tulane University Health Sciences Center, New Orleans, LA, US

Brooks Mitchell
University of Hawaii, Honolulu, HI, US

Bastiaan Moesker
University of Southampton, Southampton, UK

Samantha Molsberry
University of Pittsburgh, Pittsburgh, PA, US

Marion Morgand
Université François Rabelais, Tours, France

Masahiko Mori
Institution of Tropical Medicine, Nagasaki University, Nagasaki City, Japan

Darren Moss
University of Liverpool, Liverpool, UK

Sikhulile Moyo
Botswana-Harvard AIDS Institute, Gaborone, Botswana

Kenneth Mugwanya
University of Washington, Seattle, WA, US

Andrew Mujugira
University of Washington, Seattle, WA, US

Lyle Murray
Oxford University, Oxford, UK

Ben Murrell
University of California San Diego, La Jolla, CA, US

Laura Musselwhite
Duke University, Durham, NC, US

Philip Mwimanzi
Simon Fraser University, Burnaby, BC, Canada

Geetha Mylvaganam
Emory University, Atlanta, GA, US

Anushka Naidoo
Centre for the AIDS Programme of Research in South Africa, Durban, South Africa

Elizabeth Nalintya
Infectious Disease Institute, Kampala, Uganda

Rhoda Namakula
Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda

Venkata Narla
University of California San Francisco, San Francisco, CA, US

Maria Nevot
IrsiCaixa, Badalona, Spain

Laura Newman
University of Washington, Seattle, WA, US

Paul Alain Ngoupo
Centre Pasteur du Cameroun, Yaounde, Cameroon

Corinna Oberle
University Hospital Zurich, Zurich, Switzerland

Jane O'Halloran
University College Dublin, Dublin, Ireland

Samson Okello
Mbarara University of Science & Technology, Mbarara, Uganda

Adeniyi Olagunju
University of Liverpool, Liverpool, UK

Edmund Osei-Kuffour
Heinrich Heine University Düsseldorf, Düsseldorf, Germany

Laurence Palk
University of California Los Angeles, Los Angeles, CA, US

Claudia Palladino
University of Lisbon, Lisbon, Portugal

Clovis Palmer
Burnet Institute, Melbourne, Sydney, NSW, Australia

Theppharit Panichsillapakit
Siriraj Hospital, Mahidol University, Bangkok, Thailand

Alexander Pasternak
Academic Medical Center of the University of Amsterdam, Amsterdam, Netherlands

Eshan Patel
National Institute of Allergy and Infectious Diseases, Baltimore, MD, US

Brendan Payne
Newcastle University, Newcastle, UK

Luxin Pei
National Institutes of Health, Bethesda, MD, US

Michael Peluso
Harvard University, Boston, MA, US

Josué Pérez-Santiago
University of California San Diego, San Diego, CA, US

Maria Pernas
Instituto de Salud Carlos III, Campus de Majadahonda, Madrid, Spain

Samuel Pierre
Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections, Port-au-Prince, Haiti

Maria Pino
IrsiCaixa AIDS Research Institute, Badalona, Spain

Sandra Pinto Cardoso
Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico

Marilia Pinzone
University of Catania, Catania, Italy

Christopher Pohlmeyer
Johns Hopkins Medical Institution, Baltimore, MD, US

Benjamin Policicchio
University of Pittsburgh, Pittsburgh, PA, US

Marc Potempa
University of North Carolina, Chapel Hill, NC, US

Pavan Puligujja
University of Nebraska Medical Center, Omaha, NE, US

Nitisha Pyndiah
Institute of Microbiology, Lausanne, Switzerland

Beth Rachlis
Academic Model Providing Access to Healthcare, Eldoret, Kenya

Jessica Radzio
Centers for Disease Control and Prevention, Atlanta, GA, US

Manon Ragonnet-Cronin
University of Edinburgh, Edinburgh, UK

Elham Rahimy
Yale University School of Medicine, New Haven, CT, US

Julia Raifman
Harvard School of Public Health, Boston, MA, US

Kaitlin Rainwater-Lovett
Johns Hopkins University School of Medicine, Baltimore, MD, US

Shruthi Ravimohan
University of Pennsylvania, Philadelphia, PA, US

Sanam Razeghi
University of Cincinnati, Cincinnati, OH, US

Brian Reardon
University of California San Diego, La Jolla, CA, US

Lucia Reh
University of Zurich, Zurich, Switzerland

Joshua Rhein
University of Minnesota, Minneapolis, MN, US

Elizabeth Richards
National Institutes of Health, Bethesda, MD, US

Maureen Richards
Rush University, Chicago, IL, US

Antonio Rivero-Juarez
Instituto Maimonides de Investigación Biomédica de Cordoba, Cordoba, Spain

Prakit Riyaten
Institut de Recherche pour le Développement, Chiang Mai, Thailand

Danielle Robbins
University of California Los Angeles, Los Angeles, CA, US

Sarah Roberts
University of Washington, Seattle, WA, US

Muntsa Rocafort
IrsiCaixa, Badalona, Spain

Sara Rodriguez-Mora
Instituto de Salud Carlos, Madrid, Spain

Julia Rohr
Boston University, Boston, MA, US

Casper Rokx
Erasmus Medical Center, Rotterdam, Netherlands

Laura Romas
University of Manitoba, Winnipeg, MB, Canada

Joseph Rower
University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, US

Debbie Ruelas
University of California San Francisco, Gladstone Institute, San Bruno, CA, US

Lene Ryom Nielsen
Copenhagen HIV Programme, Department of Infectious Diseases and Rheumatology, Copenhagen, Denmark

Sara Saberi
University of British Columbia, Vancouver, BC, Canada

Talía Sainz
Hospital Universitario Gregorio Marañón, Madrid, Spain

Luisa Salazar-Vizcaya
University of Bern, Bern, Switzerland

Maria Salgado
IrisCaixa AIDS Research Institute, Badalona, Spain

Jorge Salinas
Emory University, Decatur, GA, US

Amanda Samarawickrama
Brighton and Sussex Medical School, London, UK

Luca Sardo
National Cancer Institute, Frederick, MD, US

Deanna Saylor
Johns Hopkins University School of Medicine, Baltimore, MD, US

Sheree Schwartz
Johns Hopkins University, Baltimore, MD, US

James Scriven
Liverpool School of Tropical Medicine, Sutton Coldfield, UK

Sharon Seifert
University of Colorado Denver, Aurora, CO, US

Sergio Serrano-Villar
University Hospital Ramón y Cajal, Madrid, Spain

Liang Shan
Yale University, New Haven, CT, US

Amit Sharma
Fred Hutchinson Cancer Research Center, Seattle, WA, US

Souradet Shaw
University of Manitoba, Winnipeg, MB, Canada

Ivy Shih
The Kirby Institute, Sydney, Australia

Mohaned Shilaih
University Hospital Zurich, Zurich, Switzerland

Rupak Shivakoti
Johns Hopkins University, Baltimore, MD, US

Sreetha Sidharthan
National Institutes of Health, Baltimore, MD, US

Ruth Simmons
Medical Research Council Clinical Trials Unit, University College London, London, UK

Arjun Sinha
University of California San Francisco, San Francisco, CA, US

Jennifer Smith
Imperial College London, London, UK

Kaku So-Armah
Yale University School of Medicine, New Haven, CT, US

Djadé Soumana
University of Massachusetts Medical School, Worcester, MA, US

Vincenzo Spagnuolo
San Raffaele Scientific Institute, Milan, Italy

Chelsea Spragg
Fred Hutchinson Cancer Research Center, Seattle, WA, US

Suman Srinivasa
Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

Patumrat Sripan
Institut de Recherche Pour le Développement, Chiang Mai, Thailand

Metodi Stankov
Hannover Medical School, Hannover, Germany

Guadalupe Suarez
Instituto de Investigaciones Biomédicas en Retrovirus y Sida, Buenos Aires, Argentina

Talia Swartz
Icahn School of Medicine at Mount Sinai, New York, NY, US

Carmen Teodorof
University of California San Diego, San Diego, CA, US

Kristof Theys
Rega Institute, University of Leuven, Leuven, Belgium

Aurielle Thomas
National Institutes of Health, Bethesda, MD, US

Corbin Thompson
University of North Carolina at Chapel Hill, Chapel Hill, NC, US

Kerry Thomson
University of Washington, Seattle, WA, US

Willard Tinago
University College Dublin, Dublin, Ireland

Marcel Tongo Passo
International Centre for Genetic Engineering and Biotechnology, Cape Town, South Africa

Kerry Townsend
National Institutes of Health, Baltimore, MD, US

Marina Tuyishime
Drexel University, Philadelphia, PA, US

Priyanka Uprety
Johns Hopkins University, Baltimore, MD, US

Kimyata Valere
Rutgers University, Willingboro, NJ, US

Renee van der Sluis
University of Melbourne, Melbourne, Australia

Rosan van Zoest
Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands

Joost Vanhommerig
Public Health Service of Amsterdam, Amsterdam, Netherlands

Susanna Var
University of California San Diego Center for AIDS Research, La Jolla, CA, US

Homero Vazquez
University of California San Diego, La Jolla, CA, US

Jaime Vera
Imperial College London, London, UK

Selena Vigano
Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard, Boston, MA, US

Michael Vinikoor
University of North Carolina at Chapel Hill, Chapel Hill, NC, US

Serena Vita
Sapienza University, Rome, Italy

Andrej Vitomirov
University of California San Diego, La Jolla, CA, US

Thomas Vollbrecht
University of California San Diego, La Jolla, CA, US

Susanne von Stockenstrom
Karolinska Institutet, Stockholm, Sweden

Joshua Walker
Boston College, Chestnut Hill, MA, US

Naomi Walker
Imperial College London, Wolverhampton, UK

Victoria Walker-Sperling
Johns Hopkins University School of Medicine, Baltimore, MD, US

Yuge Wang
University of Alabama at Birmingham, Birmingham, AL, US

Valentine Wanga
Vanderbilt University School of Medicine, Nashville, TN, US

Sarah Watters
National Cancer Institute, Frederick, MD, US

Cory White
University of California San Diego, La Jolla, CA, US

Ellen White
Medical Research Council Clinical Trials Unit, University College London, London, UK

Kate Wilson
University of Washington, Seattle, WA, US

Lianna Wood
Seattle BioMed, Seattle, WA, US

Patrick Wright
Washington University in St Louis, St Louis, MO, US

Julia Wu
Harvard University, Boston, MA, US

Lifei Yang
University of Washington, Seattle, WA, US

Elizabeth Yanik
National Cancer Institute, Rockville, MD, US

Christina Yek
University of California San Diego, San Diego, CA, US

Guohua Yi
Texas Tech University Health Sciences Center, El Paso, TX, US

Roger Ying
University of Washington, Bellevue, WA, US

Sunnie Yoh
Sanford Burnham Medical Institute, La Jolla, CA, US

Noriyoshi Yoshinaga
Kyoto University, Kyoto-shi, Japan

Cindy Zahnd
University of Bern, Bern, Switzerland

Rebecca Zash
Beth Israel Deaconess Medical Center, Boston, MA, US

Isaac Zentner
Drexel University College of Medicine, Philadelphia, PA, US

Jennifer Zerbato
University of Pittsburgh, Pittsburgh, PA, US

INTERNATIONAL SCHOLARSHIP AWARDEES

Anchalee Avihingsanon
HIV-NAT, Thai Red Cross AIDS Research Centre, Pathumwan, Thailand

Andrew Kambugu
Infectious Diseases Institute, Makerere University, Kampala, Uganda

Bhavna Chohan
Kenya Medical Research Institute, Seattle, WA, US

Davis Muganzi
Médecins Sans Frontières, Epicentre Mbarara Research Base, Kampala, Uganda

Irene Njuguna
University of Nairobi, Nairobi, Kenya

Johanna Ledwaba
National Institute for Communicable Diseases, Sandringham, South Africa

Judy Orikiiriza
Infectious Diseases Institute, Kampala, Uganda

Karen Cohen
University of Cape Town, Cape Town, South Africa

Linda Barlow-Mosha
Makerere University–Johns Hopkins University Research, Kampala, Uganda

Mahsa Abassi
University of Minnesota, Newport Beach, CA, US

Marika Karchava
Infectious Diseases, AIDS and Clinical Immunology, Tbilisi, Georgia

Mutsa Bwakura Dangarembizi
University of Zimbabwe College of Health Sciences, Harare, Zimbabwe

Nicolas Salvadori
International Research Development– Program for HIV Prevention and Treatment, Chiang Mai, Thailand

Paolo Denti
University of Cape Town, Cape Town, South Africa

Rebecca Berhanu
Right to Care, Framingham, MA, US

Rosalind Parkes-Ratanshi
Infectious Diseases Institute, Kampala, Uganda

Shanmugam Saravanan
Y. R. Gladstone Center for AIDS Research and Education, Chennai, India

Surasak Wiboonchutikul
Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand

Thresia Sebastian
International Center for AIDS Care and Treatment Programs, Maputo, Mozambique

Vivian Avelino-Silva
University of Sao Paulo Medical School, Sao Paulo, Brazil

Zaza Ndhlovu
Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard, Cambridge, MA, US

Cissy Kityo
Joint Clinical Research Center, Kampala, Uganda

Rita Dadaille
GHESKIO Centers, Port-au-Prince, Haiti

COMMUNITY EDUCATOR SCHOLARSHIP AWARDEES

Ferenc Bagyinszky
Hungarian Civil Liberties Union, Budapest, Hungary

Giorgio Barbareschi
European AIDS Treatment Group, Brussels, Belgium

Tamás Bereczky
European AIDS Treatment Group, Budapest, Hungary

Kate Borloglou
The Well Project, Hilliard, OH, US

Charles Brown
Infectious Diseases Institute, Kampala, Uganda

Danielle Campbell
Black AIDS Institute, Los Angeles, CA, US

Christopher Cannon
HealthHIV, Washington, DC, US

Caitlin Conyngham
Philadelphia FIGHT, Philadelphia, PA, US

John Curry
Unconditional Love, Inc, Melbourne, FL, US

Michael Dorosh
Treatment Education Network, Denver, CO, US

Florita Durueke
New HIV Vaccine and Microbicides Advocacy Society, Lagos, Nigeria

Anna Forbes
Kensington, MD, US

Gerald Garth
Black AIDS Institute, Los Angeles, CA, US

Marine Gogia
Georgian Harm Reduction Network, Tbilisi, Georgia

Joseph Hall
District of Columbia Veterans Affairs Medical Center, Washington, DC, US

Angel Hernandez
AIDS Clinical Trial Group–Community Scientific Subcommittee, Orocovis, PR, US

Courtney Johnson
American Indian Community House, Bronx, NY, US

Brian Kanyemba
Desmond Tutu HIV Foundation, Cape Town, South Africa

Sandris Klavins
AGIHAS, Riga, Latvia

Tapiwanashe Kujinga
Pan-African Treatment Access Movement, Harare, Zimbabwe

William Larson
Allina Health, Minneapolis, MN, US

Nichole Little
AIDS Vaccine Advocacy Coalition, Oakland, CA, US

Sharon Maxwell Henkel
Southwestern Illinois HIV Care Connect, Beckemeyer, IL, US

Michael Meulbroek
Asociación para el Trasplante de Órganos a Seropositivos, Barcelona, Spain

Kennedy Mupeli
Center for Youth of Hope, Gaborone, Botswana

Robert Newells
Imani Community Church, Oakland, CA, US

Nathan Nhlane
Zambia National Antiretroviral Support Programme, Lusaka, Zambia

Adeolu Ogunrombi
Youthrise Nigeria, Abuja, Nigeria

David Palm
University of North Carolina, Research Triangle Park, NC, US

Jeffrey Pope
AIDS Vaccine Advocacy Coalition, Tallahassee, FL, US

Ferran Pujol Roca
Projecte dels NOMS-Hispanosida, Barcelona, Spain

Rodney Rousseau
University of Toronto, Toronto, ON, Canada

Jorge Saz Berges
Joves Positius, Barcelona, Spain

Matt Sharp
Shanti Project, Berkeley, CA, US

Cedric Sturdevant
My Brother's Keeper, Inc, Ridgeland, MS, US

Pamela Tshandu
Wits Health Consortium, Johannesburg, South Africa

DeShawn Usher
New York Blood Center, New York, NY, US

Erik Valera
Latino Commission on AIDS, Chapel Hill, NC, US

Octavio Vallejo
AIDS Project Los Angeles, Los Angeles, CA, US

Carol Wanguwabo
Hôpital Provincial du Nord Kivu, Goma, Congo

Michael Webb
Legacy Community Health Services, Houston, TX, US

Brian West
European AIDS Treatment Group, Edinburgh, UK

Lisa Diane White
SisterLove, Inc, Atlanta, GA, US

Jens Wilhelmsborg
HIV Denmark, Copenhagen, Denmark

ORAL SESSIONS

MONDAY, FEBRUARY 23, 2015

Session W1 Workshop — Room 6E

9:00 am – 12:30 pm

Program Committee Workshop for New Investigators and Trainees

Target audience: This workshop is directed toward new trainees (eg, undergraduate students, graduate students, postdoctoral fellows, and physician fellows) and new investigators (both international and domestic).

Level of knowledge: It is assumed that participants have been conducting active research in the field for less than 3 years.

Objectives: At the completion of the session, participants will be able to:

- Describe the major areas of HIV investigation being presented at the conference.
- Identify the top 3 to 5 research questions in the field of retroviruses and opportunistic infections today.
- Describe some of the proposed solutions for addressing the challenges presented globally by a variety of retroviruses and opportunistic infections.

Workshop Conveners

Scott M. Hammer, *Columbia University Medical Center/New York-Presbyterian Hospital, New York, NY, US*

John W. Mellors, *University of Pittsburgh, Pittsburgh, PA, US*

1 A Path to an HIV Vaccine
Galit Alter
Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, US

2 Animal Models of HIV Prevention and Cure
Guido Silvestri
Emory University, Decatur, GA, US

3 HIV Prevention 2.0: What's Next?
Susan P. Buchbinder
San Francisco Department of Public Health, San Francisco, CA, US

4 Pathogenesis of HIV Complications
Peter W. Hunt
University of California San Francisco, San Francisco, CA, US

5 HIV Cure Research
John M. Coffin
Tufts University, Boston, MA, US

Session MD Presentation — Room 6E

1:00 pm – 2:00 pm

Martin Delaney Presentation: How to End the HIV Epidemic: Community Perspectives

6 Martin Delaney Presentation: How to End the HIV Epidemic: Community Perspectives

Moderator

Steven F. Wakefield, *HIV Vaccine Trials Network, Fred Hutchinson Cancer Research Center, Seattle, WA, US*

Panelists

Connie Celum, *University of Washington, Seattle, WA, US*

Damon L. Jacobs, *Private Practice Psychotherapist, Brooklyn, NY, US*

Matthew V. Sharp, *Shanti Project, Berkeley, CA, US*

Session W2 Workshop — Room 6E

2:30 pm – 4:30 pm

Clinical Trial Design and Analysis

Target audience: This session is directed to clinicians and scientists who are interested in designing or interpreting clinical trial results.

Level of knowledge: It is assumed that participants are familiar with the basic design of randomized and observational clinical studies.

Objectives: At the completion of the session, participants will be able to:

- Describe strategies for evaluating the effectiveness of interventions.
- Interpret adherence measures.
- Evaluate study design with infrequent endpoints.

Workshop Conveners

Susan P. Buchbinder, *San Francisco Department of Public Health, San Francisco, CA, US*

Richard E. Chaisson, *The Johns Hopkins University, Baltimore, MD, US*

7 Getting SMART About Innovative Designs for Studying Effectiveness: The Case of Adaptive Implementation Interventions
Daniel Almirall
University of Michigan, Ann Arbor, MI, US

8 The Clinical Pharmacology of Medication Adherence
Terrence Blaschke
Stanford University, Stanford, CA, US

9 Epidemiological and Biostatistical Issues in Studying Rare Events in HIV
Stephen J. Gange
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

Session W3 Workshop — Room 6D

2:30 pm – 4:30 pm

Frontiers in Laboratory Science

Target audience: This session is directed to investigators and clinicians interested in learning about the main technological and conceptual developments in life sciences that are influencing HIV research or hold a significant potential for research.

Level of knowledge: It is assumed that participants are familiar with the main technological and data analysis approaches used in HIV research.

Objectives: At the completion of the session, participants will be able to:

- Recognize the potential of and directions in the field of big data analysis.
- Describe developments in immunophenotyping and in single-cell analyses.
- Use the basic concepts of integration site analysis to understand current directions in HIV latency research.

Workshop Conveners

Galit Alter, *Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard University, Cambridge, MA, US*

Amalio Telenti, *The J. Craig Venter Institute, La Jolla, CA, US*

10 **Measuring Immunity 1 Cell at a Time**
Mario Roederer
Vaccine Research Center, NIAID, NIH, Bethesda, MD, US

11 **Studying Heterogeneity With Single Cell RNA-Sequencing**
Simon Quenneville
Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

12 **Integration-Site Analysis**
Frederic D. Bushman
University of Pennsylvania School of Medicine, Philadelphia, PA, US

13 **Discovery and Modeling of Genomic Regulatory Networks With Big Data**
Hamid Bolouri
Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US

Session W4 Workshop — Room 613

2:30 pm – 4:30 pm

Hepatitis C Care in the Interferon-Free Era

Target audience: This session is directed to persons interested in the management of hepatitis C virus (HCV) infection.

Level of knowledge: It is assumed that participants are familiar with the general principles of HCV treatment and the medications used.

Objectives: At the completion of the session, participants will be able to:

- Compare the various methods to stage liver disease.
- Describe the differences and similarities in treatment of HIV/HCV-coinfected persons.
- Recognize how treatment differs for persons with cirrhosis.

Workshop Conveners

Jürgen K. Rockstroh, *University of Bonn, Bonn, Germany*

David L. Thomas, *The Johns Hopkins University, Baltimore, MD, US*

14 **Acute HCV: Is It Still Important to Diagnose and Treat?**
Arthur Y. Kim
[1]Harvard Medical School, Boston, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

15 **Chronic Genotype 1 Infection**
Debika Bhattacharya
University of California Los Angeles CARE Center, Los Angeles, CA, US

16 **HCV Genotype 3: Our Next Challenge**
Arthur Y. Kim
Massachusetts General Hospital, Boston, MA, US

17 **HCV Cirrhotics With Early Decompensation**
Marion G. Peters
University of California San Francisco, San Francisco, CA, US

Opening Session — 4AB Auditorium

5:00 pm – 7:00 pm

Welcome: Opening Session

Opening Session Hosts

Scott M. Hammer, *Columbia University Medical Center/ New York-Presbyterian Hospital, New York, NY, US*

Julie M. Overbaugh, *Fred Hutchinson Cancer Research Center, Seattle, WA, US*

Susan P. Buchbinder, *San Francisco Department of Public Health, San Francisco, CA, US*

Session NL1 Lecture — 4AB Auditorium

Bernard Fields Lecture

18 **Hepatitis C: Light at the End of the Tunnel**
Charles M. Rice
The Rockefeller University, New York, NY, US

Session NL2 Lecture — 4AB Auditorium

N'Galy-Mann Lecture

19 **Antiretroviral Therapy: Past, Present, and Future**
David A. Cooper
Kirby Institute, University of New South Wales, Sydney, Australia

TUESDAY, FEBRUARY 24, 2015

Session PL-1 Plenary — 4AB Auditorium

8:30 am – 9:00 am

PrEP for HIV Prevention: What We Know and What We Still Need to Know for Implementation

20 **PrEP for HIV Prevention: What We Know and What We Still Need to Know for Implementation**

Raphael J. Landovitz

University of California Los Angeles, Los Angeles, CA, US

Session PL-2 Plenary — 4AB Auditorium

9:00 am – 9:30 am

Specific HIV Integration Sites Linked to Clonal Expansion and Persistence of Cells

21 **Specific HIV Integration Sites Linked to Clonal Expansion and Persistence of Cells**

Stephen H. Hughes

National Cancer Institute, Frederick, MD, US

Session O-1 Oral Abstracts — Room 6AB

10:00 am – 12:15 pm

Preventing HIV and HSV-2: What Will It Take?

Moderators

Sharon L. Hillier, *Magee-Womens Hospital of UPMC, University of Pittsburgh, Pittsburgh, PA, US*

Jorge Sanchez, *Impacta Peru CTU, Barranco, Peru*

22LB **Pragmatic Open-Label Randomised Trial of Preexposure Prophylaxis: The PROUD Study**

Sheena McCormack; David Dunn
On behalf of the PROUD Study Group

MRC Clinical Trials Unit at University College London, London, United Kingdom

23LB **On Demand PrEP With Oral TDF-FTC in MSM: Results of the ANRS Ipergay Trial**

Jean-Michel Molina[1]; Catherine Capitant[2]; Bruno Spire[3]; Gilles Pialoux[4]; Christian Chidiac[5]; Isabelle Charreau[2]; Cecile Tremblay[7]; Laurence Meyer[2]; Jean-Francois Delfraissy[6]
On behalf of the ANRS Ipergay Study Group

[1]University of Paris Diderot, Paris, France; [2]Inserm SC10 US019, Villejuif, France; [3]Inserm U912, Marseille, France; [4]Hopital Tenon, APHP, Paris, France; [5]Hopital de la Croix Rousse, Lyon, France; [6]ANRS, Paris, France; [7]CHUM, Montreal, Canada

24 **Near Elimination of HIV Transmission in a Demonstration Project of PrEP and ART**

Jared Baeten[1]; Renee Heffron[1]; Lara Kidoguchi[1]; Nelly Mugo[2]; Elly Katabira[3]; Elizabeth Bukusi[2]; Stephen Asiimwe[4]; Jessica Haberer[5]; Deborah Donnell[6]; Connie Celum[1]

[1]University of Washington, Seattle, WA, US; [2]Kenya Medical Research Institute, Nairobi, Kenya; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]Kabwohe Clinical Research Centre, Kabwohe, Uganda; [5]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [6]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US

25 **Scale-Up of Preexposure Prophylaxis in San Francisco to Impact HIV Incidence**

Robert M. Grant[3]; Albert Liu[2]; Jen Hecht[4]; Susan P. Buchbinder[2]; Shannon Weber[1]; Pierre-Cedric Crouch[4]; Steven Gibson[4]; Stephanie Cohen[2]; David Glidden[1]

[1]University of California San Francisco (UCSF), San Francisco, CA, US; [2]San Francisco Department of Public Health, San Francisco, CA, US; [3]Gladstone Institutes, San Francisco, CA, US; [4]San Francisco AIDS Foundation, San Francisco, CA, US

26LB **FACTS 001 Phase III Trial of Pericoital Tenofovir 1% Gel for HIV Prevention in Women**

Helen Rees[1]; Sinead A. Delany-Moretlwe[1]; Carl Lombard[2]; Deborah Baron[1]; Ravindre Panchia[4]; Landon Myer[3]; Jill L. Schwartz[5]; Gustavo F. Doncel[5]; Glenda Gray[2]
On behalf of the FACTS 001 Study Team

[1]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa; [2]South African Medical Research Council, Cape Town, South Africa; [3]University of Cape Town, Cape Town, South Africa; [4]Perinatal HIV Research Unit, Soweto, South Africa; [5]CONRAD, Arlington, VA, US

27 **Effect of Oral and Gel Tenofovir on Genital HSV Shedding in Immunocompetent Women**

Rachel A. Bender Ignacio[1]; Tara Perti[2]; Amalia S. Magaret[1]; Sharanya Rajagopal[1]; Meei-Lee W. Huang[1]; Christine M. Johnston[1]; Stacy Selke[1]; Jeanne M. Marrazzo[1]; Anna Wald[1]

[1]University of Washington, Seattle, WA, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

28 **Injectable Hormonal Contraception Use and Women's Risk for HSV-2 Acquisition**

Mary K. Grabowski[1]; Ronald H. Gray[1]; Fred Makumbi[2]; Joseph Kagaayi[2]; Andrew D. Redd[3]; Fred Nalugoda[2]; Maria J. Wawer[1]; David Serwadda[4]; Thomas C. Quinn[3]; Aaron A. Tobian[5]

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]Rakai Health Sciences Program, Kalisizo, Uganda; [3]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US; [4]Makerere University College of Health Sciences, Kampala, Uganda; [5]Johns Hopkins University, Baltimore, MD, US

29 **Effect of Financial Incentives on Linkage to Care and Viral Suppression: HPTN 065**

Wafaa M. El-Sadr[1]; Bernard M. Branson[2]; Gheetha Beauchamp[3]; H. Irene Hall[2]; Lucia V. Torian[4]; Barry S. Zingman[5]; Garret Lum[6]; Rick Elion[7]; Theresa Gamble[8]; Deborah Donnell[3]

[1]ICAP at Columbia University, New York, NY, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [3]SCHARP, Fred Hutchinson Cancer Research Center, Seattle, WA, US; [4]New York City Department of Health and Mental Hygiene, New York, NY, US; [5]Montefiore Medical Center, University Hospital for Albert Einstein College of Medicine, New York, NY, US; [6]District of Columbia Department of Health, Washington, DC, US; [7]Whitman-Walker Health, Washington, DC, US; [8]FHI360, Durham, NC, US

30 **Medical Male Circumcision of HIV-Infected Men Reduces Long-Term Penile HIV Shedding**

Jordyn L. Manucci[1]; Godfrey Kigozi[3]; Mary K. Grabowski[2]; David Serwadda[3]; Ronald H. Gray[2]; Maria J. Wawer[2]; Fred Nalugoda[3]; Andrew D. Redd[4]; Thomas C. Quinn[4]; Aaron A. Tobian[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, DC, US

Session O-2 Oral Abstracts — Room 613

10:00 am – 12:00 pm

Prevention, Diagnosis, and Treatment of Pediatric HIV Infection

Moderators

Carey Farquhar, *University of Washington, Seattle, WA, US*

Annette H. Sohn, *TREAT Asia/amfAR – The Foundation for AIDS Research, Bangkok, Thailand*

31LB **PROMISE: Efficacy and Safety of 2 Strategies to Prevent Perinatal HIV Transmission**

Mary Glenn Fowler[1]; Min Qin[2]; Susan A. Fiscus[3]; Judith S. Currier[4]; Bonus Makanani[5]; Francis Martinson[6]; Tsungai Chipato[7]; Renee Browning[8]; David Shapiro[2]; Lynne Mofenson[9]
On Behalf of the IMPAACT PROMISE Team

[1]Johns Hopkins University School of Medicine/Makerere University, Baltimore, MD, US; [2]Harvard School of Public Health, Boston, MA, US; [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, US; [4]University of California Los Angeles, Los Angeles, CA, US; [5]Univ of Malawi, Blantyre, Malawi; [6]University of North Carolina Project–Malawi, Lilongwe, Malawi; [7]Univ of Zimbabwe, Harare, Zimbabwe; [8]NIAID/NIH, Bethesda, MD, US; [9]National Institute of Child Health and Human Development, Bethesda, MD, US

32 Most Breastfeeding Women With High Viral Load Are Still Undiagnosed in Sub-Saharan Africa

David Maman[1]; Helena Huerga[1]; Irene Mukui[4]; Benson Chilima[2]; Beatrice Kirubi[5]; Gilles Van Cutsem[6]; Charles Masiku[7]; Elisabeth Szumilin[8]; Thomas Ellman[3]; Jean-François Etard[1]

[1]Epicentre/Médecins Sans Frontières, Paris, France; [2]3. Ministry of Health, Lilongwe, Malawi; [3]Medecins Sans Frontières, Cape Town, South Africa; [4]National AIDS and STDs Control Program, Nairobi, Kenya; [5]Médecins Sans Frontières, Nairobi, Kenya; [6]Médecins Sans Frontières, Cape Town, South Africa; [7]Médecins Sans Frontières, Lilongwe, Malawi; [8]Médecins Sans Frontières, Paris, France

33 Delayed HIV Detection in Infants Exposed to ARV Prophylaxis During Breastfeeding

Caroline C. King[1]; Julie A. Nelson[2]; Carrie Ziemniak[3]; Michael G. Hudgens[2]; Gerald Tegha[4]; Charles S. Chasela[5]; Denise J. Jamieson[1]; Deborah Persaud[3]; Charles M. van der Horst[2]; Athena P. Kourtis[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, US; [3]Johns Hopkins University, Baltimore, MD, US; [4]UNC Project, Lilongwe, Malawi; [5]University of Witwatersrand, Johannesburg, South Africa

34 Evaluation of the Alere q for Point-of-Care Early Infant HIV Diagnosis in South Africa

Nei-Yuan Hsiao[1]; Max Kroon[2]; Lorna Dunning[2]; Landon Myer[2]

[1]University of Cape Town, Cape Town, South Africa; [2]University of Cape Town, Cape Town, South Africa

35 Early ART and Sustained Virological Suppression Limits HIV Proviral DNA Reservoir: CHER Evidence

Helen A. Payne[1]; Sarah Watters[1]; Marvin Hsaio[2]; Robin Callard[1]; Abdel Babiker[3]; Mark F. Cotton[4]; Kennedy Otwombe[5]; Avy Violari[5]; Diana M. Gibb[3]; Nigel J. Klein[1]

[1]University College London, London, United Kingdom; [2]University of Cape Town, Cape Town, South Africa; [3]MRC Clinical Trials Unit at University College London, London, United Kingdom; [4]Stellenbosch University, Cape Town, South Africa; [5]University of Witswatersrand, Johannesburg, South Africa

36 Long-Term Outcomes of HIV-Infected Children Initiating NVP vs LPV/r-Based Treatment

Linda Barlow-Mosha[1]; Konstantia Angelidou[2]; Moherndran Archary[8]; Avy Violari[7]; Jane Lindsey[2]; Lynne Mofenson[3]; Patrick Jean-Philipe[5]; Paul E Palumbo[4]; Benjamin Chi[6]
On behalf of the IMPAACT P1060 Protocol Team

[1]Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]National Institutes of Health, Bethesda, MD, US; [4]Geisel School of Medicine at Dartmouth, Lebanon, NH, US; [5]Henry M. Jackson Foundation for the Advancement of Military Medicine, Rockville, MD, US; [6]University of North Carolina at Chapel Hill, Chapel Hill, NC, US; [7]University of Witswatersrand, Johannesburg, South Africa; [8]University of KwaZulu-Natal, Durban, South Africa; [9]IMPAACT, SilverSpring, MD, US

37 Structural Cardiovascular Changes Are Reversible in HIV-Infected Children in Zambia and Uganda.

Julia M. Kenny[1]; Adrian Cook[1]; Grace Mirembe[2]; Dorica Masaku[3]; Priscilla Wavamunno[2]; Florence Odongo[2]; Alicja Rapala[1]; John Deanfield[1]; Diana M. Gibb[1]; Nigel J. Klein[1]

[1]University College London, London, United Kingdom; [2]Joint Clinical Research Centre, Kampala, Uganda; [3]University Teaching Hospital, Lusaka, Zambia

38LB ART With Weekends Off Is Noninferior to Continuous ART in Young People on EFV+2NRTI

Karina M. Butler
On behalf of the BREATHER Trial Team

Our Lady's Children's Hospital, Dublin, Ireland

Session O-3 Oral Abstracts — Room 615

10:00 am – 12:00 pm

Cellular Dynamics, Sensing, and Viral Restriction

Moderators

Jaisri Lingappa, *University of Washington, Seattle, WA, US*

Aine McKnight, *Queen Mary University of London, London, United Kingdom*

39 Envelope Trimer Numbers Required for Entry Steer HIV-1 Infectivity and Entry Kinetics

Oliver Brandenberg[2]; Carsten Magnus[2]; Peter Rusert[2]; Roland Regoes[1]; **Alexandra Trkola**[2]

[1]ETH Zurich, Zurich, Switzerland; [2]University of Zurich, Zurich, Switzerland

40 HIV-1 Accessory Protein Function: Evaluating VPU-Dependent Host Factor Degradation

Prashant Jain; Kevin Olivieri; Quy Nguyen; Paul De Jesus; Sumit Chanda

Sanford-Burnham Medical Research Institute, La Jolla, CA, US

41 HIV-1 Adaptation to Humans Involved Interactions of Vpr With the DNA Damage Response

Oliver I. Fregoso; Michael Emerman

Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US

42 The HIV-1 Protease Can Interact With RNA to Dramatically Enhance Its Activity

Marc Potempa[1]; Ellen Nalivaika[2]; Sook-Kyung Lee[1]; Celia A. Schiffer[2]; Ronald Swanstrom[1]

[1]University of North Carolina, Chapel Hill, NC, US; [2]University of Massachusetts Medical School, Worcester, MA, US

43 PQBP1 Is a Retrovirus-Specific Sensor Mediating cGAS/IRF3-Dependent Innate Responses

Sunnie M. Yoh[1]; Monika Schneider[1]; Stephen Soonthornvarcharin[1]; Rana Akleh[1]; Kevin Olivieri[1]; Paul De Jesus[1]; Chunhai Ruan[2]; Elisa de Castro[3]; Pedro Ruiz[1]; Adolfo Garcia-Sastre[3]

[1]Sanford-Burnham Medical Research Institute, La Jolla, CA, US; [2]University of Michigan, Ann Arbor, MI, US; [3]Icahn School of Medicine at Mount Sinai, New York, NY, US

44 Mucosal HIV-1 Transmission Specifically Selects for Type 1 Interferon-Resistant Viruses

Shilpa Iyer[1]; Frederic Bibollet-Ruche[1]; Christiana M. Shaw[1]; Weiyu Zhang[1]; Yingying Li[1]; Timothy Decker[1]; George M. Shaw[1]; Persephone Borrow[2]; Beatrice H. Hahn[1]

[1]University of Pennsylvania, Philadelphia, PA, US; [2]University of Oxford, London, United Kingdom

45 The Dynamics of HIV-1 RNA Near the Plasma Membrane During Virus Assembly

Luca Sardo; Steven C. Hatch; Jianbo Chen; Olga A. Nikolaitchik; Ryan C. Burdick; De Chen; Christopher J. Westlake; Stephen Lockett; Vinay K. Pathak; Wei-Shau Hu

Frederick National Laboratory for Cancer Research, Frederick, MD, US

46LB Mechanisms of Dendritic Cell-Mediated Transfer of HIV-1 to CD4$^+$T Lymphocytes

Mickael M. Menager[1]; Wendy Lin[1]; Jarrod S. Johnson[2]; Kristen Dancel-Manning[1]; Nicolas Manel[3]; Feng-Xia Liang[1]; Dan R. Littman[1]

[1]Skirball Institute of Biomolecular Medicine, New York, NY, US; [2]Seattle Biomedical Research Institute, Seattle, WA, US; [3]Institut Curie, Paris, France

Session O-4 Oral Abstracts — Room 6D

10:00 am – 12:15 pm

New Discoveries in HIV Pathogenesis

Moderators

Irini Sereti, *National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US*

Donald Sodora, *Seattle Biomed, Seattle, WA, US*

47 Inflammation Persists Despite Early Initiation of ART in Acute HIV Infection

Netanya S. Utay[1]; Jintanat Ananworanich[2]; Suteera Pinyakorn[3]; Adam Rupert[5]; Duanghathai Sutthichom[3]; Suwanna Puttamaswin[3]; Bonnie M. Slike[2]; Nelson L. Michael[2]; Daniel C. Douek[4]; Irini Sereti[4]

[1]University of Texas Medical Branch at Galveston, Galveston, TX, US; [2]US Military HIV Research Program, Silver Spring, MD, US; [3]South East Asia Research Collaboration with Hawaii, Bangkok, Thailand; [4]National Institutes of Health (NIH), Frederick, MD, US; [5]Leidos Biomedical Research, Inc, Frederick, MD, US

48 HIV Burden and Biomarker Associations With Colonic HIV RNA During Acute HIV Infection

James L. Fletcher[2]; **Trevor A. Crowell**[1]; Robin Dewar[3]; Irini Sereti[4]; Bonnie Slike[1]; Nitiya Chomchey[2]; Rungsun Rerknimitr[5]; Nelson L. Michael[1]; Nicolas Chomont[6]; Jintanat Ananworanich[1]
On behalf of the RV254/SEARCH010 Study Group

[1]US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, US; [2]SEARCH, Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [3]Virus Isolation and Serological Lab, National Cancer Institute at Frederick, Frederick, MD, US; [4]National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, MD, US; [5]Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [6]Vaccine and Gene Therapy Institute Florida, Port St. Lucie, FL, US

49 Identification and Characterization of Individual HIV-Infected CD4 T Cells Ex Vivo

Joseph Casazza[1]; Irene Primmer[1]; David Ambrozak[1]; Constantinos Petrovas[1]; Sara Ferrando-Martinez[1]; Perla Del Río-Estrada[2]; Gustavo Reyes-Terán[2]; Ezequiel Ruiz-Mateos[3]; John Mascola[1]; Richard A. Koup[1]

[1]Vaccine Research Center, NIAID, NIH, Bethesda, MD, US; [2]Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico; [3]HU Virgen del Rocio/IBIS, Sevilla, Spain

50 Efficacy of HIV-1 Monoclonal Antibody Immunotherapy in Acute SHIV-Infected Macaques

Diane L. Bolton[1]; Amarendra Pegu[2]; Keyun Wang[2]; Kathleen McGinnis[2]; Kathryn Foulds[2]; Srinivas Rao[2]; Merlin L. Robb[1]; Nelson L. Michael[1]; John Mascola[2]; Richard A. Koup[2]

[1]US Military HIV Research Program, Silver Spring, MD, US; [2]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

51 HIV-1 Infections With Multiple Founders Are Associated With Higher Viral Loads

Holly Janes[1]; Sodsai Tovanabutra[2]; Joshua Herbeck[3]; Supachai Rerks-Ngarm[4]; Merlin L. Robb[2]; Nelson L. Michael[2]; Peter Gilbert[1]; Jerome H. Kim[2]; **Morgane Rolland**[2]
On behalf of the Step/HVTN502 and RV144 study teams

[1]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [2]US Military HIV Research Program, Silver Spring, MD, US; [3]University of Washington, Seattle, WA, US; [4]Thai Ministry of Public Health, Bangkok, Thailand

52 Post-Treatment Controllers Have Particular NK Cells With High Anti-HIV Capacity: VISCONTI Study

Daniel Scott-Algara[1]; Céline Didier[1]; Vincent Arnold[1]; Jean-Saville Cummings[1]; Faroudy Boufassa[2]; Olivier Lambotte[3]; Laurent Hocqueloux[4]; Asier Sáez-Cirión[1]; Christine Rouzioux[3]

[1]Institut Pasteur, Paris, France; [2]CESP U1018 Inserm, Le Kremlin-Bicêtre, France; [3]Laboratoire de Virologie, EA 3620–Université Paris Descartes Hôpital Necker, Paris, France; [4]Service des Maladies Infectieuses et Tropicales CHR d'Orléans–La Source, Orleans, France; [5]Hôpital Bicêtre, Le Kremilin-Bicêtre, France

53 Antiretroviral Therapy Preserves Polyfunctional HIV-1–Specific CD8 T Cells With Stem-Cell–Like Properties

Selena Vigano[1]; Jordi J. Negron[1]; Eric S. Rosenberg[2]; Bruce D. Walker[1]; Mathias Lichterfeld[2]; Xu G. Yu[1]

[1]The Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

54LB In Vitro Replication and Interferon-Alpha Resistance of Transmitted HIV-1 Variants

Zachary Ende[1]; Martin Deymier[1]; Angharad Fenton-May[2]; Daniel T. Claiborne[1]; William Kilembe[3]; Susan Allen[1]; Persephone Borrow[2]; Eric Hunter[1]

[1]Emory University, Atlanta, GA, US; [2]Oxford University, Oxfordshire, United Kingdom; [3]Zambia Emory HIV Research Project, Lusaka, Zambia

55LB HVTN505 Breakthrough Sequences Show HIV Vaccine-Associated Differences in Env-gp120

Morgane Rolland[1]; Allan deCamp[2]; Breana M. Hall[3]; Sodsai Tovanabutra[1]; Mario Roederer[4]; Scott M. Hammer[5]; Magdalena E. Sobieszczyk[5]; Peter B. Gilbert[2]; Jerome H. Kim[6]; James Mullins[3]
On behalf of the HVTN505 Sieve Analysis Group

[1]US Military HIV Research Program; Henry M. Jackson Foundation for the Advancement of Military Medicine Inc, Silver Spring, MD, US; [2]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [3]University of Washington, Seattle, WA, US; [4]Vaccine Research Center, Bethesda, MD, US; [5]Columbia University, New York, NY, US; [6]US Military HIV Research Program, Silver Spring, MD, US

Session TD-B Themed Discussion — Room 615

1:30 pm – 2:30 pm

Next Generation of Next-Generation Sequencing

Themed Discussion Leader

Davey M. Smith, *University of California San Diego, San Diego, CA, US*

258 PCR-Free Full Genome Characterization of Diverse HIV-1 Strains by Nextgen Sequencing

Viswanath Ragupathy[1]; Feng Gao[2]; Ana Sanchez[2]; Marco Schito[3]; Thomas Denny[2]; Michael Busch[4]; Jiangqin Zhao[1]; Christelle Mbondji[1]; SaiVikram Vemula[1]; Indira Hewlett[1]

[1]US Food and Drug Administration, Silver Spring, MD, US; [2]Duke Human Vaccine Institute and Departments of Medicine, Duke University Medical Center, Durham, NC, US; [3]Henry Jackson Foundation, DAIDS, NIAID, Bethesda, MD, US; [4]Blood Systems Research Institute/University of California San Francisco, San Francisco, CA, US

257 Pan-HIV Next-Gen Sequencing Strategy for Viral Surveillance

Michael G. Berg[1]; Julie Yamaguchi[1]; Elodie Alessandri-Gradt[2]; Jean-Christophe Plantier[2]; Catherine Brennan[1]

[1]Abbott Laboratories, Abbott Park, IL, US; [2]Virology Unit, National Reference for HIV, Rouen, France

256 Near Full Length HIV-1 Sequencing to Understand HIV Phylodynamics in Africa in Real Time

Siva Danaviah; Justen Manasa; Eduan Wilkinson; Sureshnee Pillay; Zandile Sibisi; Sthembiso Msweli; Deenan Pillay; **Tulio de Oliveira**

University of KwaZulu-Natal, Durban, South Africa

254 Present Applications of a High-Throughput, Single Measure HIV Genomic Incidence Assay

Sung Yong Park[1]; Tanzy Love[2]; Nolan Goeken[1]; Robert Bolan[3]; Alan S Perelson[4]; Michael Dube[1]; **Ha Youn Lee**[1]

[1]Keck School of Medicine at University of Southern California, Los Angeles, CA, US; [2]University of Rochester School of Medicine and Dentistry, Rochester, CA, US; [3]Los Angeles Gay and Lesbian Center, Los Angeles, CA, US; [4]Los Alamos National Laboratory, Los Alamos, CA, US

255 A Comprehensive Analysis of Primer IDs to Study Heterogenous HIV-1 Populations

David Seifert[1]; Armin Töpfer[1]; Francesca Di Giallonardo[2]; Stefan Schmutz[2]; Huldrych F. Günthard[2]; Volker Roth[3]; Niko Beerenwinkel[1]; Karin J. Metzner[2]

[1]ETH Zurich, Basel, Switzerland; [2]University Hospital Zurich, Zurich, Switzerland; [3]University of Basel, Basel, Switzerland

593 Analysis of Resistance Haplotypes Using Primer IDs and Next Gen Sequencing of HIV RNA

Valerie F. Boltz[1]; Jason Rausch[1]; Wei Shao[2]; Charles Coomer[1]; John W. Mellors[3]; Mary Kearney[1]; John M. Coffin[4]

[1]National Institutes of Health (NIH), Frederick, MD, US; [2]Leidos, Frederick, MD, US; [3]University of Pittsburgh, Pittsburgh, PA, US; [4]Tufts University, Boston, MA, US

Session TD-C Themed Discussion — Room 613

1:30 pm – 2:30 pm

HIV/CMV Interactions in Transmission and Pathogenesis

Themed Discussion Leader

Victor Appay, *Institut National de la Santé et de la Recherche Médicale, Paris, France*

300 Effect of CMV and HIV Replication on T-Cell Exhaustion and Senescence During ART

Jennifer M. Dan[1]; Marta Massanella[1]; David M. Smith[1]; Eric S. Daar[2]; Michael P. Dube[3]; Richard Haubrich[1]; Sheldon Morris[1]; Sara Gianella Weibel[1]

[1]University of California San Diego, La Jolla, CA, US; [2]Harbor–University of California Los Angeles Medical Center, Torrance, CA, US; [3]University of Southern California Keck School of Medicine, Los Angeles, CA, US

301 HIV Myeloid Derived Suppressor Cells Control Cytomegalovirus Inflammation by IL-27

Ankita Garg; Stephen Spector

University of California San Diego, La Jolla, CA, US

302 Persistent Elevation of Inflammation Markers in HIV+ Persons With CMV Disease

Melissa Schechter[1]; Bruno Andrade[2]; Eleanor M. Wilson[1]; Virginia Sheikh[2]; Sonya Krishnan[2]; Margaret Caplan[1]; Gregg Roby[2]; Adam Rupert[3]; Peter Burbelo[4]; Irini Sereti[2]

[1]NIAID, Leidos Biomedical Inc., Fredrick, MD, US; [2]National Institute of Allergy and Infectious Diseases, Bethesda, MD, US; [3]NIAID, Leidos Biomedical Inc., Fredrick, MD, US; [4]National Institute of Dental and Craniofacial Research, Bethesda, MD, US

303 sCD163 Increase in HIV/CMV-Coinfected Subjects Included in ICONA Cohort

Serena Vita[3]; Miriam Lichtner[1]; Giulia Marchetti[2]; Claudia Mascia[3]; Esther Merlini[2]; Paola Cicconi[2]; Vincenzo Vullo[3]; Pier Luigi Viale[5]; Alberto Costantini[4]; Antonella d'Arminio Monforte[2]
On behalf of the Icona Foundation Study

[1]University of Rome La Sapienza, Polo Pontino, Latina, Italy; [2]San Paolo Hospital, Milano, Italy; [3]University of Rome La Sapienza, Rome, Italy; [4]University of Ancona, Ancona, Italy; [5]University of Bologna, Bologna, Italy

304 Genital CMV Shedding Predicts Syphilis Acquisition in HIV-Infected MSM on ART

Sara Gianella Weibel[1]; David M. Smith[1]; Eric Daar[2]; Michael Dube[3]; Andrea Lisco[4]; Christophe Vanpouille[5]; Richard Haubrich[1]; Sheldon Morris[1]

[1]University of California San Diego, La Jolla, CA, US; [2]Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, US; [3]University of Southern California Keck School of Medicine, Los Angeles, CA, US; [4]National Institute of Allergy and Infectious Diseases, Bethesda, MD, US; [5]National Institute of Child Health and Human Development, Bethesda, MD, US

Session TD-F Themed Discussion — Room 6D

1:30 pm – 2:30 pm

Leaky Latency

Themed Discussion Leader

Monique Nijhuis, *University Medical Center Utrecht, Utrecht, Netherlands*

392 Defective HIV-1 Proviruses Can Be Transcribed Upon Activation

Ya-Chi Ho; Ross Pollack; Patrick Yong; Robert F. Siliciano

Johns Hopkins University School of Medicine, Baltimore, MD, US

391 Influenza Vaccination Increases HIV-1 Transcription During Antiretroviral Therapy

Christina C. Yek[1]; Sara Gianella[1]; Montserrat Plana[2]; Pedro Castro[2]; Felipe Garcia[2]; Marta Massanella[1]; David M. Smith[1]

[1]University of California San Diego, San Diego, CA, US; [2]University of Barcelona, Barcelona, Spain

427 Measurements of Viral Transcription in Elite Suppressor CD4+ T Cells

Christopher W. Pohlmeyer; C. Korin Bullen; Greg Laird; Alyssa R. Martin; Victoria Walker-Sperling; Stanley U. Chioma; Robert F. Siliciano; Joel Blankson

Johns Hopkins University School of Medicine, Baltimore, MD, US

384 Minor Contribution of Host-HIV Readthrough Transcripts to the Level of HIV-1 *gag* RNA

Alexander Pasternak[1]; Una O'Doherty[2]; Ben Berkhout[1]

[1]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [2]University of Pennsylvania, Philadelphia, PA, US

379 Characterizing the Active HIV Reservoir on ART: Cell-Associated HIV RNA and Viremia

Feiyu Hong; Elizabeth Fyne; Anthony R. Cillo; Margaret A. Bedison; Dianna Koontz; John W. Mellors

University of Pittsburgh, Pittsburgh, PA, US

390 Nascent LTR-Driven Transcription Can Lead to Translation of HIV Proteins in Resting CD4+ T Cells

Laura DeMaster[1]; Alexander Pasternak[2]; Una O'Doherty[1]

[1]University of Pennsylvania, Philadelphia, PA, US; [2]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands

Session TD-Q Themed Discussion — Room 6AB

1:30 pm – 2:30 pm

Fat Without Borders: Metabolic Complications in Resource-Limited Settings

Themed Discussion Leader

Miriam Rabkin, *Columbia University Mailman School of Public Health, Chapel Hill, NC, US*

778 Obesity and Inflammation in Resource-Diverse Settings of ART Initiation

Kristine M. Erlandson[1]; Nikhil Gupte[2]; Javier R. Lama[3]; Patcharaphan Sugandhavesa[4]; Thando Mwelase[5]; Ashwin Balagopal[2]; David Asmuth[6]; Thomas B. Campbell[1]; Amita Gupta[2]
On behalf of the A5175 and NWCS319 study team

[1]University of Colorado, Aurora, CO, US; [2]Johns Hopkins University, Baltimore, MD, US; [3]Impacta Peru Clinical Trials Unit, Lima, Peru; [4]Chiang Mai University, Chiang Mai, Thailand; [5]University of Witswatersrand, Johannesburg, South Africa; [6]University of California Davis, Sacramento, CA, US

779 Body Composition Outcomes at 96 Weeks in the SECOND-LINE RCT DXA Substudy

Mark A. Boyd[1]; Janaki Amin[1]; Patrick W. Mallon[2]; Jennifer F. Hoy[3]; Samuel Ferret[4]; Waldo Belloso[5]; Praphan Phanuphak[6]; Sean Emery[1]; David A. Cooper[1]
On behalf of the SECOND-LINE study group

[1]University of New South Wales Australia, Sydney, Australia; [2]University College Dublin, Dublin, Ireland; [3]Monash University/Alfred Hospital, Melbourne, Australia; [4]Hopital Saint Louis, Paris, France; [5]Hospital Italiano, Buenos Aires, Argentina; [6]Thai Red Cross AIDS Research Centre, Bangkok, Thailand

780 Bone Quality by Quantitative Ultrasound at the Radius Does Not Differ in ART-Naïve HIV+ and HIV- Rwandan Women

Eugene Mutimura[1]; Qiuhu Shi[2]; Donald R. Hoover[3]; Kathryn Anastos[4]; Emmanuel Rudakemwa[5]; Jean Claude Dusingize[1]; Jean D'Amour Sinayobye[1]; Michael T Yin[6]

[1]Regional Alliance for Sustainable Development, Kigali, Rwanda; [2]School of Health Sciences and Practice, New York Medical College, New York, NY, US; [3]State University of New Jersey, New Brunswick, NJ, US; [4]Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, US; [5]King Faisal Hospital, Kigali, Rwanda; [6]Columbia University Medical Center, New York, NY, US

781 Predictors and Outcomes of Incident High Cholesterol in Adults on ART in South Africa

Denise Evans[1]; Alana T. Brennan[2]; Faith Moyo[1]; David Spencer[3]; Kay Mahomed[3]; Mhairi Maskew[1]; Lawrence Long[1]; Sydney Rosen[2]; **Matt P. Fox**[2]

[1]University of the Witwatersrand, Johannesburg, South Africa; [2]Boston University, Boston, MA, US; [3]Right to Care, Johannesburg, South Africa

782 Metabolic Changes and Second-Line ART in Africa (2LADY/ANRS 12169 Trial)

Amandine Cournil[1]; Assane Diouf[3]; Sabrina Eymard-Duvernay[1]; Adrien Sawadogo[2]; Liliane Ayangma[4]; Louise Fortes-Deguenonvo[3]; Jean-Marc Mben[6]; Eric Delaporte[1]; Laura Ciaffi[1]; Sinata Koulla-Shiro[5]

[1]IRD/UM 1, Montpellier, France; [2]CHU Souro Sanou, Bobo Dioulasso, Burkina Faso; [3]CRCF, Dakar, Senegal; [4]Yaounde Military Hospital, Yaounde, Cameroon; [5]FMSB/University Yaounde 1, Yaounde, Cameroon; [6]ANRS Research Center, Yaounde, Cameroon

Session TD-S Themed Discussion — Room 6C

1:30 pm – 2:30 pm

Hormonal Contraceptives: Enduring Controversy

Themed Discussion Leader

Betsy Herold, *Albert Einstein College of Medicine, Bronx, NY, US*

859 Estrogen Replacement in Healthy Postmenopausal Women Reduces %CCR5+ CD4+ T Cells

Amie Meditz[1]; Samantha MaWhinney[2]; Kerrie Moreau[2]; Kelsey Melander[2]; Joy Folkvord[2]; Wendy Kohrt[2]; Margaret Wierman[2]; Elizabeth Connick[2]

[1]Boulder Community Health, Boulder, CO, US; [2]University of Colorado Anschutz Medical Campus, Aurora, CO, US

858 CCR5 Expression in HIV-Uninfected Women Receiving Hormonal Contraception

Athe Tsibris[1]; Gaia Sciaranghella[2]; Cuiwei Wang[3]; Kerry Murphy[4]; Zaher Mehri[5]; Ruth M. Greenblatt[6]; Mardge Cohen[7]; Elizabeth Golub[8]; Heather Watts[9]; Mary A. Young[3]

[1]Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, US; [2]Ragon Institute of MIT, MGH and Harvard, Boston, MA, US; [3]Georgetown University Medical Center, Washington, DC, US; [4]Albert Einstein College of Medicine, Bronx, NY, US; [5]University of Vermont College of Medicine, Burlington, VT, US; [6]University of California San Francisco, San Francisco, CA, US; [7]Stroger Hospital and Rush University and CORE Center, Chicago, IL, US; [8]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [9]The Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US

860 Progesterone Increases Are Associated With HIV Susceptibility Factors in Women

Alison Y. Swaims[1]; Tammy Evans-Strickfaden[1]; L Davis Lupo[1]; Alfredo Aguirre[2]; Anandi Sheth[2]; Igho Ofotokun[2]; Clyde E. Hart[1]; **Richard E. Haaland**[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]Emory University School of Medicine, Atlanta, GA, US

861 Changes in Vaginal Microbiota and Cytokines in HIV-1-Seronegative Women Initiating DMPA

Alison C. Roxby[1]; David N. Fredricks[2]; Katherine Odem-Davis[1]; Kristjana H. Ásbjörnsdóttir[1]; Linnet Masese[1]; Tina L. Fiedler[2]; Walter Jaoko[3]; James N. Kiarie[3]; Julie M. Overbaugh[2]; R Scott McClelland[1]

[1]University of Washington, Seattle, WA, US; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [3]University of Nairobi, Nairobi, Kenya

Session TD-Y Themed Discussion — Room 6E

1:30 pm – 2:30 pm

Circumcision: Evolving Knowledge and Practice

Themed Discussion Leader

Emmanuel Njeuhmeli, *US Agency for International Development (USAID), Douglasville, GA, US*

1086 Mobile VMMC Teams in Tanzania See Older Clients and Have Higher Followup Rates

Augustino M. Hellar[1]; Dorica Boyee[1]; Hally Mahler[1]; Marya Plotkin[1]; Touma Ng'wanakilala[1]; Kelly Curran[2]; Tigistu Ashengo[2]; Hawa Mziray[1]; Erick Mlanga[3]; Sifuni Koshuma[4]

[1]Jhpiego, Dar es Salaam, United Republic of Tanzania; [2]Jhpiego, Baltimore, MD, US; [3]US Agency for International Development, Dar es Salaam, United Republic of Tanzania; [4]Ministry of Health and Social Welfare, Iringa, United Republic of Tanzania

1087 High Acceptability of PrePex™ Device in Routine Programmatic Settings in Rwanda

Eugene Rugwizangoga[1]; Beata Mukarugwiro[1]; Jovite Sinzahera[1]; Alphonse Mutabaruka[1]; Gloriose Abayisenga[1]; J.D. Ntakakirabose[1]; Ngeruka Leon[4]; Eugene Zimulinda[3]; Kelly Curran[2]; Tigistu Ashengo[2]

[1]Jhpiego/Rwanda, Kigali, Rwanda; [2]Jhpiego, an Affiliate of Johns Hopkins University, Washington, DC, US; [3]US Department of Defense, Rwanda, Kigali, Rwanda; [4]Rwanda Military Hospital, Kigali, Rwanda

1089 Potential Protection From HIV Transmission by Penile Cuttings in Papua New Guinea

Ivy H. Shih[1]; Lester Asugeni[2]; Matthew David[5]; Paul Horwood[5]; Parana Hewage Mangalasir[3]; David Mc Laren[3]; Rachael Tommbe[2]; Andrew Vallely[1]; Arnold Waine[4]; Stuart G. Turville[1]

[1]The Kirby Institute, Sydney, Australia; [2]Pacific Adventist University, Port Moresby, Papua New Guinea; [3]James Cook University, Cairns, Australia; [4]University of Papua New Guinea, Port Moresby, Papua New Guinea; [5]Papua New Guinea Institute of Medical Health, Goroka, Papua New Guinea

1084 HSV-2 Shedding From Male Circumcision Wounds Among HIV-Infected Men

Mary K. Grabowski[1]; Godfrey Kigozi[2]; Ronald H. Gray[1]; Jordyn L. Manucci[3]; David Serwadda[4]; Eshan U. Patel[3]; Fred Nalugoda[2]; Maria J. Wawer[1]; Thomas C. Quinn[5]; Aaron A. Tobian[3]

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]Rakai Health Sciences Program, Kalisizo, Uganda; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]Makerere University College of Health Sciences, Kampala, Uganda; [5]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

1088 Self-Selection of Circumcision Acceptors, Risk Compensation and Effectiveness of Circumcision Among Service Recipients, Rakai, Uganda

Joseph Kagaayi[1]; Xiangrong Kong[2]; Godfrey Kigozi[1]; Fred Nalugoda[1]; Steven J. Reynolds[3]; David Serwadda[4]; Nelson K. Sewankambo[5]; Maria J. Wawer[2]; Ronald H. Gray[2]

[1]Rakai Health Sciences Program, Entebbe, Uganda; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, US; [4]Makerere University School of Public Health, Kampala, Uganda; [5]Makerere University College of Health Sciences, Kampala, Uganda

Session O-5 Oral Abstracts — Room 613

4:00 pm – 6:00 pm

NeuroAIDS Pathogenesis and Antiretroviral Therapy

Moderators

Lucette A. Cysique, *NeuRA, UNSW Australia, Randwick, NSW, Australia*

Alan Winston, *Imperial College London, London, United Kingdom*

56 Randomized Clinical Trial of Antiretroviral Therapy for Prevention of HAND

Fujie Zhang[1]; Robert Heaton[2]; Hao Wu[3]; Hua Jin[2]; Hongxin Zhao[4]; Xin Yu[5]; Donald Franklin[2]; Weiwei Mu[1]; Florin Vaida[2]; **Scott Letendre**[2]

[1]Chinese Center for Disease Control and Prevention, Beijing, China; [2]University of California San Diego (UCSD), San Diego, CA, US; [3]Capital Medical University, Beijing You'an Hospital, Beijing, China; [4]Capital Medical University Beijing Ditan Hospital, Beijing, China; [5]Peking University, Beijing, China

57 Neurocognitive Function in Africans Failing First-Line ART and Responses to Second Line

Andrew D. Kambugu[1]; Jennifer Thompson[2]; James Hakim[6]; Dinah Tumukunde[10]; Joep van Oosterhout[7]; Anne Hoppe[2]; Charles Kwobah[9]; Sarah Walker[2]; Nicholas Paton[8]
On behalf of the EARNEST Trial Team

[1]Infectious Diseases Institute, Makerere University Kampala, Kampala, Uganda; [2]University College London, London, United Kingdom; [3]Joint Clinical research Centre, Kampala, Uganda; [4]Queen Elizabeth Central Hospital, Malawi, Blantyre, Malawi; [5]AMPATH, Kenya, Eldoret, Kenya; [6]University of Zimbabwe, Harare, Zimbabwe; [7]Dignitas International, Zomba, Malawi; [8]National University of Singapore, Singapore, Singapore; [9]Moi University College of Health Sciences, Eldoret, Kenya; [10]Joint Clinical Research Centre, Kampala, Uganda

58 Compartmentalized HIV Rebound in the CNS After ART Interruption

Sara Gianella Weibel; Michelli Faria de Oliveira; Konrad Scheffler; Matt Strain; Antonio De la Torre; Scott Letendre; David M. Smith; Sergei L. Kosakovsky Pond; Ronald J. Ellis

University of California San Diego, La Jolla, CA, US

59 Impaired Blood-Brain Barrier Integrity Is Associated With Neuronal Injury in HIV

Birgitta Anesten[1]; Lars Hagberg[1]; Henrik Zetterberg[2]; Staffan Nilsson[3]; Bruce J. Brew[4]; Dietmar Fuchs[5]; Richard Price[6]; Magnus Gisslén[1]

[1]University of Gothenburg, Gothenburg, Sweden; [2]University of Gothenburg, Gothenburg, Sweden; [3]Mathematical Sciences, Chalmers University of Technology, Gothenburg, Sweden, Gothenburg, Sweden; [4]University of New South Wales, Sydney, Australia; [5]Division of Biological Chemistry, Biocenter, Medical University, Innsbruck, Austria, Inssbruck, Austria; [6]University of California San Francisco, San Francisco, CA, US

60 Cortical and Subcortical Brain Volumes in Primary HIV Infection

Patrick W. Wright[1]; Ashmit Pyakurel[3]; Kevin Robertson[4]; Julia Peterson[5]; Henrik Zetterberg[7]; Dietmar Fuchs[6]; Richard Price[5]; Dieter Meyerhoff[5]; Serena Spudich[2]; Beau Ances[1]

[1]Washington University School of Medicine, Saint Louis, MO, US; [2]Yale University School of Medicine, New Haven, CT, US; [3]Louisiana Tech University, Ruston, LA, US; [4]University of North Carolina, Chapel Hill, NC, US; [5]University of California San Francisco, San Francisco, CA, US; [6]Innsbruck Medical University, Innsbruck, Austria; [7]University of Gothenburg, Gothenburg, Sweden

61 IRF4 Transcription Factor Associated With Integrated HIV DNA in Brain Macrophages

Benjamin B. Gelman[1]; Joshua G. Lisinicchia[1]; Tetyana P. Buzhdygan[1]; Vipulkumar Patel[1]; Tyler Clement[1]; Samantha A. Trevino[1]; Kristofer R. Jennings[1]; Dennis L. Kolson[2]

[1]University of Texas Medical Branch, Galveston, TX, US; [2]University of Pennsylvania, Philadelphia, PA, US

62 Longitudinal Assessment of Blood Brain Barrier Disruption in Primary HIV Infection

Elham Rahimy[1]; Fang-yong Li[2]; Alex Russell[4]; Julia Peterson[4]; Lars Hagberg[3]; Henrik Zetterberg[3]; Richard Price[4]; Magnus Gisslén[3]; Serena Spudich[1]

[1]Yale University School of Medicine, New Haven, CT, US; [2]Yale Center for Analytical Sciences, Yale University, New Haven, CT, US; [3]University of Gothenburg, Gothenburg, Sweden; [4]University of California San Francisco, San Francisco, CA, US

63 Declining Prevalence of HIV-Associated Neurocognitive Disorders in More Recent Years

Carmela Pinnetti; Raffaella Libertone; Pietro Balestra; Patrizia Lorenzini; Martina Ricottini; Samanta Menichetti; Maria Maddalena Plazzi; Mauro Zaccarelli; Adriana Ammassari; Andrea Antinori

National Institute for Infectious Diseases, Lazzaro Spallanzani, Rome, Italy

Session S-1 Symposium — Room 6C

4:00 pm – 6:00 pm

Harnessing Antibodies for Prevention and Therapeutics

Target audience: This session is directed to scientists and clinicians interested in the potential therapeutic and prophylactic applications of anti-HIV antibodies.

Level of knowledge: It is assumed that participants are familiar with basic immunologic principles, antibody structure, and HIV envelope variability.

Objectives: At the completion of the session, participants will be able to:

- List cutting-edge approaches for the delivery of protective and curative antibodies.
- Describe emerging approaches to enhance monoclonal antibody activity against virus.
- Describe new advances in the ability to elicit antibodies that resemble neutralizing antibodies through vaccination.

Symposium Conveners

Leonidas Stamatatos, *Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US*

Susan Zolla-Pazner, *New York University, Langone Medical Center*

64 Potentiating Protective Antibody Activity: A Systems Serology Approach

Margaret E. Ackerman

Thayer School of Engineering, Dartmouth College, Hanover, NH, US

65 Impact of Repetitive Protein Boosting on RV305 HIV-1 Vaccine-Induced Antibodies

Georgia D. Tomaras

Duke University Medical Center, Durham, NC, US

66 Immunoprophylaxis by Gene Transfer: Shortcut to an HIV Vaccine

Phil Johnson

Children's Hospital of Philadelphia, Philiadlphia, PA, US

67 Broadly Neutralizing Antibodies for HIV-1 Eradication Strategies

Dan H. Barouch

Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US

Session S-2 Symposium — Room 6D

4:00 pm – 6:00 pm

Current Issues in HIV-Related Malignancies

Target audience: This session is directed to those interested in development and management of cancers in HIV.

Level of knowledge: It is assumed that participants have some basic knowledge of types of cancers seen in HIV.

Objectives: At the completion of the session, participants will be able to:

- Discuss differences in malignancy incidence and presentation, including in resource-limited settings around the world.
- Describe new concepts in viral-induced oncogenesis.
- Describe new therapies for lymphoma in HIV-infected individuals.
- Examine major barriers for treatment of cancers in resource-limited settings.

Symposium Conveners

Margaret Z. Borok, *University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe*

Robert Yarchoan, *National Cancer Institute, Bethesda, MD, US*

68 HIV-Associated Malignancies: The Worldwide Epidemic

James J. Goedert

National Cancer Institute, Bethesda, MD, US

69 Viral Oncogenesis: Evolving Concepts

Shannon C. Kenney

University of Wisconsin, Madison, WI, US

70 AIDS Lymphoma: Advances and Existing Challenges

Ariela Noy

Memorial Sloan Kettering Cancer Center, New York, NY, US

71 HIV Malignancies in Low- and Middle-Income Countries: A Double Burden of Disease

Jackson Orem

Uganda Cancer Institute, Kampala, Uganda

Session S-3 Symposium — Room 6AB

4:00 pm – 6:00 pm

Current Imperatives in HIV Prevention and Treatment

Target audience: This session is directed to researchers, public health professionals, and educators interested in global HIV and public health.

Level of knowledge: It is assumed that participants are familiar with HIV program scale-up and global disease burden.

Objectives: At the completion of the session, participants will be able to:

- Define trends in HIV/AIDS and sexually transmitted infection epidemiology among different groups.
- Describe the epidemiology of HIV among men who have sex with men in Africa, and associated challenges.
- Assess broader impact on health programs and behavioral science of HIV/AIDS service scale-up.

Symposium Conveners

Wafaa M. El-Sadr, *ICAP at Columbia University, New York, NY, US*

Lucy Ng'ang'a, *CDC Center for Global Health, Division of Global AIDS/HIV, Nairobi, Kenya*

72 How Has HIV Prevention Affected the Spread of Other Sexually Transmitted Infections?

Marie Laga

Institute of Tropical Medicine, Antwerp, Belgium

73 HIV Risks and Vulnerabilities Among Gay Men and Other Men Who Have Sex With Men Across Sub-Saharan Africa

Stefan Baral

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

74 An Expanded Behavioral Paradigm for Treatment and Prevention of HIV-1

Thomas J. Coates

University of California Los Angeles, Los Angeles, CA, US

75 Social Protection, Financial Incentives, and Prevention of HIV

David Wilson

World Bank, Washington, DC, US

Special Session **Room 6E**

6:30 pm – 7:30 pm

Special Session: Ebola Virus Disease: Responding to the Challenge

Moderators

Kevin M. De Cock, *Centers for Disease Control and Prevention, Nairobi, Kenya*

Wafaa M. El-Sadr, *ICAP at Columbia University, New York, NY, US*

76 **The Médecins Sans Frontières Experience With the Current Ebola Outbreaks**

Gilles Van Cutsem

Médecins Sans Frontières, Mowbray, Cape Town, South Africa

77 **Ebola Treatment and Vaccine Development and Implementation: Challenges and Opportunities**

H. Clifford Lane

National Institute of Allergy and Infectious Diseases, Bethesda, MD, US

WEDNESDAY, FEBRUARY 25, 2015

Session PL-1 Plenary — 4AB Auditorium

8:30 am – 9:00 am

Preventing Pediatric HIV and Managing HIV-Infected Children: Where Are We Now and Where Are We Going?

78 **Preventing Pediatric HIV and Managing HIV-Infected Children: Where Are We Now, and Where Are We Going?**

Diana M. Gibb

University College London, London, United Kingdom

Session PL-2 Plenary — 4AB Auditorium

9:00 am – 9:30 am

Directing Chronic Virus Infection Through Viral Regulation of Innate Immune Defenses

79 **Directing Chronic Virus Infection Through Viral Regulation of Innate Immune Defenses**

Michael Gale

University of Washington, Center for Innate Immunity and Immune Disease, Seattle, WA, US

Session O-6 Scientific Overview and Oral Abstracts — Room 615

10:00 am – 12:00 pm

Intracellular and Clinical Pharmacology, Drug Interactions, and Adherence

Moderators

Reina Bendayan, *University of Toronto, Toronto, ON, Canada*

Marta Boffito, *Chelsea and Westminster Hospital, NHS Foundation Trust/Imperial College, London, United Kingdom*

80 **Scientific Overview: The Clinical Pharmacology of HIV Prevention**

Marta Boffito

Chelsea and Westminster Hospital, NHS Foundation Trust/Imperial College, London, United Kingdom

81 **Intracellular Pharmacokinetics of Sofosbuvir In Vivo**

Joseph Rower[1]; Ariel Hodara[1]; Jacob A. Langness[3]; Sarah Tise[1]; Greg Everson[1]; Aimee Truesdale[2]; Fafa Baouchi-Mokrane[2]; Lane Bushman[1]; Peter L. Anderson[1]; Jennifer J. Kiser[1]

[1]University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, US; [2]Denver Health and Hospital Authority, Denver, CO, US; [3]University of Colorado Health, Aurora, CO, US; [4]University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, US

82 **Drug-Drug Interactions Between Anti-HCV Regimen Ledipasvir/Sofosbuvir and Antiretrovirals**

Polina German; Kimberly Garrison; Phillip S. Pang; Luisa M. Stamm; Adrian S. Ray; Gong Shen; Marc Buacharern; Anita Mathias

Gilead Sciences, Inc., Foster City, CA, US

83 **Emtricitabine-Triphosphate in Dried Blood Spots (DBS) as a Marker of Recent Dosing**

Jose R. Castillo-Mancilla[1]; Lane R. Bushman[1]; Amie Meditz[2]; Sharon M. Seifert[1]; Jia-Hua Zheng[1]; L Anthony Guida[1]; Edward M. Gardner[3]; David V. Glidden[4]; Robert M. Grant[4]; Peter L. Anderson[1]

[1]University of Colorado-AMC, Aurora, CO, US; [2]Beacon Center for Infectious Diseases, Boulder, CO, US; [3]Denver Health and Hospital Authority, Denver, CO, US; [4]University of California San Francisco, San Francisco, CA, US

84 **Impact of EFV PK/PG on Neuropsychological Performance in Older HIV+ Patients**

Uriel S. Sandkovsky[1]; Anthony T. Podany[1]; Courtney Fletcher[1]; Andrew Owen[2]; Angela Felton-Coleman[1]; Kevin Robertson[3]; Susan Swindells[1]

[1]University of Nebraska Medical Center, Omaha, NE, US; [2]University of Liverpool, Liverpool, United Kingdom; [3]University of North Carolina, Chapel Hill, NC, US

85LB **Levonorgestrel Implant + EFV-Based ART: Unintended Pregnancies and Associated PK Data**

Kimberly K. Scarsi[1]; Kristin M. Darin[3]; Shadia Nakalema[2]; David Back[4]; Pauline Byakika-Kibwika[2]; Laura Else[4]; Sujan Dilly-Penchala[4]; Susan Cohn[3]; Concepta Merry[5]; Mohammed Lamorde[2]

[1]University of Nebraska Medical Center, Omaha, NE, US; [2]Infectious Diseases Institute, Kampala, Uganda; [3]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [4]University of Liverpool, Liverpool, United Kingdom; [5]Trinity College Dublin, Dublin, Ireland

86LB **A Phase IV PrEP Study Reveals Limited Ex Vivo Potency of Oral Maraviroc Against HIV-1**

Julie Fox[1]; Carolina Herrera[2]; Juan Manuel Tiraboschi[1]; Akil Jackson[3]; Laura Else[4]; Natalia Olejniczak[2]; Saye Khoo[4]; David Back[4]; Robin Shattock[2]; Marta Boffito[3]
On behalf of KCL Infectious Diseases Biobank

[1]Guys and St Thomas' NHS Foundation Trust, London, United Kingdom; [2]Imperial College London, London, United Kingdom; [3]Chelsea and Westminster Hospital, NHS Foundation Trust, London, United Kingdom; [4]University of Liverpool, Liverpool, United Kingdom

Session O-7 Oral Abstracts — Room 613

10:00 am – 12:15 pm

KS and Cervical/Anal Dysplasia: Tale of 2 Tumors, and TB and Other OIs

Moderators

Corey Casper, *Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US*

Timothy Sterling, *Vanderbilt University, Nashville, TN, US*

87 **Pomalidomide for Kaposi Sarcoma in People With and Without HIV: A Phase I/II Study**

Mark N. Polizzotto[1]; Thomas S. Uldrick[1]; Kathleen M. Wyvill[1]; Karen Aleman[1]; Margaret Bevans[2]; Cody Peer[1]; Douglas Figg[1]; Seth Steinberg[1]; Jerome B. Zeldis[5]; Robert Yarchoan[1]

[1]National Cancer Institute (NCI), Bethesda, MD, US; [2]National Institutes of Health (NIH), Bethesda, MD, US; [3]National Cancer Institute (NCI), Bethesda, MD, US; [4]National Cancer Institute (NCI), Bethesda, MD, US; [5]Celgene Corporation, Summit, NJ, US

88 **Prognostic Model for Patients With Kaposi Sarcoma Treated With ART Alone in Africa**

Miriam O. Laker-Oketta[1]; David V. Glidden[2]; Victoria Walusansa[1]; Jackson Orem[1]; A. Rain Mocello[2]; Toby Maurer[2]; Peter W. Hunt[2]; Andrew D. Kambugu[1]; Edward Mbidde[1]; **Jeffrey Martin**[2]

[1]Makerere University College of Health Sciences, Kampala, Uganda; [2]University of California San Francisco, San Francisco, CA, US; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]University of California San Francisco (UCSF), San Francisco, CA, US; [5]University of California San Francisco (UCSF), San Francisco, CA, US

89 **One-Year Follow-up of HIV+ Women Screened With VIA, Cytology and HPV in South Africa**

Cynthia Firnhaber[1]; Bridgette Goeieman[1]; Lu Mao[2]; Mark Faesen[3]; Simon Levin[3]; Sophie Williams[3]; Avril Swarts[1]; Pam Michelow[1]; Tanvier Omar[1]; Jennifer Smith[2]

[1]University of Witswatersrand, Johannesburg, South Africa; [2]University of North Carolina, Raleigh, NC, US; [3]Right to Care, Johannesburg, South Africa

90 **High Rate of HSIL on HRA in HIV+ Women Not Meeting Criteria for Anal Cancer Screening**

Michael M. Gaisa; **Fanny Ita-Nagy**; Gabriela Rodriguez Caprio; Michael Mullen; Judith Aberg; Michelle Cespedes

Icahn School of Medicine at Mount Sinai, New York, NY, US

91 **Xpert MTB/RIF Ultra: A New Near-Patient TB Test With Sensitivity Equal to Culture**

David Alland[1]; Mazhgan Rowneki[1]; Laura Smith[1]; Jamie Ryan[2]; Mitchell Chancellor[2]; Ann Marie Simmons[2]; David Persing[2]; Robert Kwiatkowski[2]; Martin Jones[2]; Soumitesh Chakravorty[1]

[1]Rutgers New Jersey Medical School, Newark, NJ, US; [2]Cepheid, Sunnyvale, CA, US

92 Majority of XDR TB Cases Are Due to Transmission in a High-HIV-Prevalence Setting

N. Sarita Shah[1]; James C. Brust[2]; Barun Mathema[3]; Thuli Mthiyane[4]; Nazir Ismail[5]; Pravi Moodley[6]; Koleka Mlisana[8]; Salim Allana[7]; Jonathan Smith[7]; Neel R. Gandhi[7]

[1]US Centers for Disease Control and Prevention, Atlanta, GA, US; [2]Montefiore Medical Center & Albert Einstein College of Medicine, Bronx, NY, US; [3]Columbia University Mailman School of Public Health, New York, NY, US; [4]University of KwaZulu-Natal, Durban, South Africa; [5]National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg, South Africa; [6]University of KwaZulu-Natal & National Health Laboratory System, Durban, South Africa; [7]Emory University Rollins School of Public Health, Atlanta, GA, US; [8]University of KwaZulu-Natal & National Health Laboratory Service, Durban, South Africa

93 Linkage to HIV/TB Care in South Africa: A Randomized Trial of Health Navigators

Ingrid V. Bassett[2]; Sharon M. Coleman[1]; Janet Giddy[4]; Laura M. Bogart[3]; Christine E. Chaisson[1]; Douglas Ross[5]; Tessa Govender[4]; Kenneth A. Freedberg[2]; Rochelle P. Walensky[2]; Elena Losina[2]

[1]Boston University School of Public Health, Boston, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Boston Children's Hospital, Harvard Medical School, Boston, MA, US; [4]McCord Hospital, Durban, South Africa; [5]St. Mary's Hospital, Mariannhill, South Africa

94 Is It Safe to Stop Cotrimoxazole in Adults on ART: COSTOP, a Noninferiority RCT

Paula Munderi[1]; **Jonathan B. Levin**[1]; Zacchaeus Anywaine[1]; Ronnie Kasirye[1]; Anatoli Kamali[1]; Andrew J. Nunn[2]; Heiner Grosskurth[3]
On behalf of COSTOP Research Team

[1]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda; [2]University College London, London, United Kingdom; [3]London School of Hygiene and Tropical Medicine, London, United Kingdom

95LB High-Dose Rifampin, SQ109 and Moxifloxacin for Treating TB: The PanACEA MAMS-TB Trial

Martin J. Boeree[1]; Michael Hoelscher[2]
On behalf of the PanACEA consortium

[1]Radboudumc, Nijmegen, Netherlands; [2]University of Munich, Munich, Germany

Session O-8 Special Presentation and Oral Abstracts — Room 6E

10:00 am – 12:15 pm

Factors Affecting HIV Care and Outcome: Global Perspective

Moderators

Ruanne V. Barnabas, *University of Washington, Seattle, WA, US*

Elizabeth Bukusi, *University of California San Francisco, San Francisco, CA, US*

96 Special Presentation: PEPFAR 3.0: Controlling the Epidemic and Delivering on the Promise of an AIDS-Free Generation

Ambassador Deborah L. Birx, MD
US Department of State, Washington, DC, US

97 Joint Estimation of HIV Progression and Survival: A Pooled Analysis of 25 Countries

Tara D. Mangal
On behalf of the UNAIDS Working Group on CD4 Progression and Mortality Among HIV Seroconverters including the CASCADE Collaboration in EuroCoord
Imperial College London, London, United Kingdom

98 Impact of Emergency Department HIV Testing and Linkage to Care: 25 Years' Experience

Gabor Kelen[3]; Eshan U. Patel[2]; Yu-Hsiang Hsieh[3]; Oliver B. Laeyendecker[2]; Judy Shahan[3]; William Clarke[3]; Jordyn L. Manucci[3]; Richard Rothman[3]; **Thomas C. Quinn**[2]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]National Institute of Allergy and Infectious Diseases (NIAID), Baltimore, MD, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US

99 Linkage to Care and Viral Suppression Among New HIV Diagnoses, New York City, 2006-13

Ellen W. Wiewel; **Lucia V. Torian**; Qiang Xia; Sarah L. Braunstein
New York City Department of Health and Mental Hygiene, Long Island City, NY, US

100 Care and Viral Suppression Among Women, 18 US Jurisdictions

Ndidi Ike; Angela L. Hernandez; Qian An; Taoying Huang; H. Irene Hall
US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

101 Time Above 1500 Copies/ml: A Viral-Load Measure for Assessing Transmission Risk of HIV-Positive Patients in Care

Lytt I. Gardner[1]; Gary Marks[1]; Charles Rose[1]; Meg Sullivan[2]; Susan Holman[3]; Jeanne Keruly[4]; Anne Zinski[5]; Allan Rodriguez[6]; Thomas Giordano[7]

[1]Centers for Disease Control and Prevention, Atlanta, GA, US; [2]Boston University School of Medicine, Boston, MA, US; [3]Colleges of Medicine and Nursing, SUNY Downstate Medical Center, Brooklyn, NY, US; [4]Johns Hopkins University School of Medicine, Baltimore, MD, US; [5]University of Alabama at Birmingham, Birmingham, AL, US; [6]Miller School of Medicine, University of Miami, Miami, FL, US; [7]Baylor College of Medicine, Houston, TX, US

102 Incidence and Risk Factors for Sexual Assault Among MSM and Young Women in Coastal Kenya

Adrian D. Smith[1]; Sam Rogers[1]; Elizabeth Wahome[2]; Marianne Darwinkel[2]; Susan M. Graham[3]; Eduard J. Sanders[2]

[1]Nuffield Department of Population Health, Oxford, United Kingdom; [2]Centre for Geographic Medicine Research – Coast, Kilifi, Kenya; [3]University of Washington, Seattle, WA, US

103LB Impact of the Ebola Epidemic on HIV Care in Macenta, Forest Guinea, 2014

David Leuenberger[1]; Jean Hébélamou[1]; Stefan Strahm[1]; Gilles Wandeler[2]; Nathalie de Rekeneire[3]; François Dabis[3]
On behalf of International Epidemiological Databases to Evaluate AIDS - West Africa

[1]Mission Philafricaine, Conakry, Guinea; [2]Department of Infectious Diseases, University Hospital Bern, Bern, Switzerland; [3]Université Bordeaux, ISPED, Centre Inserm U897-Epidemiologie-Biostatistique, Bordeaux, France

103-ALB Favipiravir in Patients with Ebola Virus Disease: Early Results of the JIKI trial in Guinea

Daouda Sissoko[1], Elin Folkesson[2], M'lebing Abdoul[3], Abdoul Habib Beavogui[4], Stephan Gunther[6], Susan Shepherd[3], Christine Danel[1],France Mentre[5], Xavier Anglaret[1], **Denis Malvy**[1]

[1]Inserm U897, Université de Bordeaux, Bordeaux, France; [2]Médecins Sans Frontières, Bruxelles, Belgium; [3]ALIMA, Montreuil, France; [4]Centre de Formation et de Recherche en Santé Rurale de Maférinyah, Conakry, Guinée; [5]Inserm U738, Université Paris Diderot, Paris, France; [6]Bernhard-Nocht-Institut für Tropenmedizin, Hamburg, Germany

Session O-9 Oral Abstracts — Room 6D

10:00 am – 12:15 pm

New Insights Into HIV Persistence, Latency Reversal, and Viremia Rebound

Moderators

Francoise Barre-Sinoussi, *Institut Pasteur*

Celsa A. Spina, *University of California San Diego, La Jolla, CA, US*

104LB Durable Control of Viral Rebound in Humanized Mice by ABX464 Targeting Rev Functions

Noelie Campos[1]; Renier Myburgh[3]; Aude Garcel[1]; Audrey Vautrin[2]; Laure Lapasset[2]; Katjana Tantale[2]; Mark Wainberg[4]; Roberto Speck[3]; Didier Scherrer[1]; **Jamal Tazi**[2]

[1]ABIVAX, Montpellier, France; [2]University of Montpellier, Montpellier, France; [3]University of Zurich, Zurich, Switzerland; [4]McGill AIDS Center, Montréal, Canada

105 Residual Viremia Caused by Clonally Expanded Tumor-Infiltrating CD4+ Cells

Francesco R. Simonetti[1]; Michele D. Sobolowski[2]; Shawn Hill[1]; Wei Shao[3]; Elizabeth Fyne[2]; Xiaolin Wu[1]; John M. Coffin[4]; Stephen H. Hughes[1]; John W. Mellors[2]; Frank Maldarelli[1]

[1]National Cancer Institute (NCI), Frederick, MD, US; [2]University of Pittsburgh, Pittsburg, PA, US; [3]Frederick National Laboratory for Cancer Research, Frederick, MD, US; [4]Tufts University, Boston, MA, US; [5]National Cancer Institute (NCI), Frederick, MD, US

106 Analysis of HIV RNA in Single Cells Reveals Clonal Expansions and Defective Genomes

Ann Wiegand[1]; Jonathan Spindler[1]; Wei Shao[2]; Feiyu Hong[3]; Anthony R. Cillo[3]; Elias Halvas[3]; Elizabeth Fyne[3]; John M. Coffin[4]; John W. Mellors[3]; **Mary F. Kearney**[1]

[1]National Cancer Institute, Frederick, MD, MD, US; [2]Leidos, Frederick, MD, US; [3]University of Pittsburgh, Pittsburgh, PA, US; [4]Tufts University, Boston, MA, US

107 Low-Level HIV Viremias Originate in Part From Infected Proliferating Cells

Marta E. Bull[1]; Sherry McLaughlin[2]; Hannah Huang[2]; Sheila Styrchak[2]; Jaime Soria[3]; Eduardo Ticona[3]; Alberto La Rosa[4]; Caroline Mitchell[5]; James Mullins[1]; Lisa Frenkel[1]

[1]University of Washington, Seattle, WA, US; [2]Seattle Children's Research Institute, Seattle, WA, US; [3]Hospital Nacional dos de Mayo, Lima, Peru; [4]Investigaciones Médicas en Salud (INMENSA), Lima, Peru; [5]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [6]University of Washington, Seattle, WA, US

108 Treatment With a TLR7 Agonist Induces Transient Viremia in SIV-Infected ART-Suppressed Monkeys

James B. Whitney[1]; So-Yon Lim[1]; Christa E. Osuna[1]; Srisowmya Sanisetty[1]; Tiffany L. Barnes[2]; Peter T. Hraber[3]; Tomas Cihlar[2]; Romas Geleziunas[2]; Joseph Hesselgesser[2]

[1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US; [2]Gilead Sciences, Inc., Foster City, CA, US; [3]Los Alamos National Laboratories, Los Alamos, NM, US

109 Panobinostat Broadly Activates Latent HIV-1 Proviruses in Patients

Kirston M. Barton[1]; Thomas A. Rasmussen[2]; Martin Tolstrup[2]; Wei Shao[4]; Bonnie Hiener[1]; Ajantha Solomon[3]; Lars Østergaard[2]; Sharon R. Lewin[3]; Ole Søgaard[2]; **Sarah E. Palmer**[1]

[1]Westmead Millennium Institute and University of Sydney, Westmead, Australia; [2]Aarhus University Hospital, Aarhus, Denmark; [3]Doherty Institute for Infection and Immunity, Melbourne, Australia; [4]National Cancer Institute, Rockville, MD, US

110LB The Size of the Active HIV Reservoir Predicts Timing of Viral Rebound

Behzad Etemad[1]; Hayat Ahmed[1]; Evgenia Aga[2]; Ronald Bosch[2]; John W. Mellors[3]; Daniel Kuritzkes[1]; Michael Para[4]; Rajesh T. Gandhi[5]; **Jonathan Li**[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]University of Pittsburgh, Pittsburgh, PA, US; [4]Ohio State University, Columbus, OH, US; [5]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

111LB Biomarkers to Predict Viral Rebound at Antiretroviral Therapy Interruption in SPARTAC

Jacob Hurst[1]; James Williams[1]; John P. Thornhill[2]; Matthew Pace[1]; Chris Willberg[1]; Elizabeth Hamlyn[3]; Abdel Babiker[4]; Rodney Phillips[1]; Sarah Fidler[2]; **John Frater**[1]
on behalf of the SPARTAC Trial Investigators

[1]University of Oxford, Oxford, United Kingdom; [2]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom; [3]King's College London, London, United Kingdom; [4]Medical Research Council Clinical Trials Unit, London, United Kingdom

112LB HIV-1 Diversity and Tropism of Rebound Virus After Treatment Discontinuation

Maria M. Bednar[1]; Blake Hauser[1]; Jeffrey M. Jacobson[2]; Ian Frank[4]; Joseph J. Eron[3]; Ronald Swanstrom[1]
On behalf of the NWCS 379 team

[1]University of North Carolina, Durham, NC, US; [2]Drexel University College of Medicine, Philadelphia, PA, US; [3]University of North Carolina, Chapel Hill, NC, US; [4]University of Pennsylvania, Philadelphia, PA, US

Session TD-A Themed Discussion — Room 615

1:30 pm – 2:30 pm

Interferon: Triggers and Effectors

Themed Discussion Leader

Martin R. Jakobsen, *Aarhus University,Aarhus C, Denmark*

188 HIV-1 Exploits CD169 to Evade IFNα-Induced Antiviral State in Myeloid Cells

Hisashi Akiyama[1]; Nora Ramirez[1]; Gregory Gibson[2]; Simon Watkins[2]; Zandrea Ambrose[2]; Rahm Gummuluru[1]

[1]Boston University School of Medicine, Boston, MA, US; [2]University of Pittsburgh School of Medicine, Pittsburgh, PA, US; [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, US

192 HIV and SIV Inhibition by RNA-Associated Early Stage Antiviral Factor (REAF)

Aine McKnight

Queen Mary University of London, London, United Kingdom

184 Regulation of the Innate Immune Sensing of HIV by the Viral Capsid and the Cytosolic DNA Sensor cGAS

Nicolas Manel

Institut Curie, Paris, France

203 Mapping Vpx and Vpr Specificity in Antagonism of SAMHD1

Chelsea Spragg; Michael Emerman

Fred Hutchinson Cancer Research Center, Seattle, WA, US

202 A Surprising New Function of SAMHD1 as a Pro-Pathogenic Factor in HIV Infection

Gilad Doitsh; Nicole Galloway; Xin Geng; Isa Monus Arias; Zhiyuan Yang; Warner C. Greene

The J. David Gladstone Institute, University of California San Francisco, San Francisco, CA, US

191 Characterization of the Activity of an Innate Immunity Protein, the Apolipoprotein L6

Nitisha Pyndiah[1]; Angela Ciuffi[1]; Amalio Telenti[2]

[1]Institute of Microbiology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [2]J Craig Venter Institute, San Diego, CA, US

Session TD-H Themed Discussion — Room 613

1:30 pm – 2:30 pm

New Technologies in Assessing Drug Interactions and Systemic and Intracellular Pharmacology

Themed Discussion Leader

Tim R. Cressey, *Harvard School of Public Health / Chiang Mai University, Chiang Mai, Thailand*

531 Pharmacokinetic Interactions Between Antidiabetics and Efavirenz Using PBPK Modeling

Catia Marzolini[1]; Rajith Rajoli[2]; Luigia Elzi[1]; Manuel Battegay[1]; David Back[2]; Marco Siccardi[2]

[1]University Hospital Basel, Basel, Switzerland; [2]Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom

532 In Silico Simulation of Interaction Between Rifampicin and Boosted Darunavir

Marco Siccardi; Owain Roberts; Rajith Rajoli; Laura Dickinson; Saye Khoo; Andrew Owen; David Back

University of Liverpool, Liverpool, United Kingdom

533 Pharmacogenetics of Pregnancy-Induced Changes in Efavirenz Pharmacokinetics

Adeniyi Olagunju[1]; Oluseye Bolaji[2]; Alieu Amara[1]; Laura Else[1]; Ogechi Okafor[3]; Ebunoluwa Adejuyigbe[2]; Oyigboja Johnson[4]; David Back[1]; Saye Khoo[1]; Andrew Owen[1]

[1]University of Liverpool, Liverpool, United Kingdom; [2]Obafemi Awolowo University, Ile-Ife, Nigeria; [3]Bishop Murray Medical Centre, Makurdi, Nigeria; [4]Catholic Caritas Foundation of Nigeria, Makurdi, Nigeria

534 Antiretroviral Drug Transporters and Metabolic Enzymes in Human Testicular Tissue

Billy Huang[1]; Md. Tozammel Hoque[1]; Mohammad-Ali Jenabian[3]; Kishanda Vyboh[2]; Nancy Sheehan[2]; Pierre Brassard[4]; Maud Bélanger[4]; Nicolas Chomont[5]; Jean-Pierre Routy[2]; Reina Bendayan[1]

[1]University of Toronto, Toronto, Canada; [2]McGill University, Montréal, Canada; [3]Université du Québec à Montréal, Montréal, Canada; [4]Metropolitan Centre of Plastic Surgery, Montréal, Canada; [5]Vaccine and Gene Therapy Institute of Florida, Port St Lucie, FL, US

535 Imaging the Spatial Distribution of Efavirenz in Intact HIV Tissue Reservoirs

Elias P. Rosen[1]; Corbin G. Thompson[2]; Mark T. Bokhart[1]; Craig Sykes[2]; Yuri Fedoriw[2]; Paul Luciw[3]; David C. Muddiman[1]; Angela D.M. Kashuba[2]

[1]North Carolina State University, Raleigh, NC, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]University of California Davis, Davis, CA, US

Session TD-O Themed Discussion — Room 6D

1:30 pm – 2:30 pm

Cancers in Young and Old, and Lung Cancer in HIV

Themed Discussion Leader

Eric A. Engels, *National Cancer Institute (NCI), Bethesda, MD, US*

724 Cancer in HIV-Infected Children: Record Linkage Study in South Africa

Julia Bohlius[6]; Nicky Maxwell[2]; Brian Eley[3]; Hans Prozesky[4]; Shobna Sawry[1]; Karl-Günter Technau[1]; Alan Davidson[2]; Cristina Stefan[5]; **Matthias Egger**[6]
On behalf of IeDEA Southern Africa

[1]University of the Witwatersrand, Johannesburg, South Africa; [2]University of Cape Town, Cape Town, South Africa; [3]Red Cross War Memorial Children's Hospital, Cape Town, South Africa; [4]University of Stellenbosch and Tygerberg Academic Hospital, Cape Town, South Africa; [5]Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa; [6]University of Bern, Bern, Switzerland

725 High Cancer Risk Among the HIV-Infected Elderly in the United States

Elizabeth L. Yanik; Hormuzd A. Katki; Eric A. Engels

National Cancer Institute (NCI), Rockville, MD, US

726 Smoking Outweighs HIV-Related Risk Factors for Non–AIDS-Defining Cancers

Keri N. Althoff[1]; Stephen J. Gange[1]; Chad Achenbach[2]; Lisa P. Jacobson[1]; Angel M. Mayor[3]; Michael J. Silverberg[4]; Amy Justice[5]; Richard Moore[6]; Yuezhou Jing[1]; Kelly Gebo[6]
On behalf of the North American AIDS Cohort Collaboration on Research and Design

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [3]Universidad Central del Caribe, Bayamon, US; [4]Kaiser Permanente Northern California, Oakland, CA, US; [5]Veterans Affairs Connecticut Healthcare System and Yale Schools of Medicine and Public Health, New Haven, CT, US; [6]Johns Hopkins University School of Medicine, Baltimore, MD, US

727 High Frequency of Early Lung Cancer Diagnosis With Chest CT in HIV-Infected Smokers

Alain Makinson[1]; Sabrina Eymard-Duvernay[2]; François Raffi[3]; Fabrice Bonnet[4]; Laurence Thirard[5]; Pierre Tattevin[6]; Sophie Abgrall[7]; Jacques Reynes[1]; Vincent Le Moing[1]
on behalf of the ANRS EP48 HIV CHEST Study Team

[1]University Hospital Montpellier, UMI233, Montpellier, France; [2]UMI 233, IRD, University Montpellier 1, Montpellier, France; [3]Nantes University Hospital, Nantes, France; [4]University Hospital Bordeaux, Inserm U897, Bordeaux, France; [5]Tourcoing University Hospital, Tourcoing, France; [6]Pontchaillou University Hospital, Rennes, France; [7]University Hospital Avicennes, Bobigny, France; [8]ANRS, Paris, France

728 CD4 Measures as Predictors of Lung Cancer Risk and Prognosis in HIV Infection

Keith Sigel[1]; Kristina Crothers[2]; Kirsha Gordon[3]; Sheldon Brown[4]; David Rimland[5]; Maria Rodriguez-Barradas[6]; Cynthia Gibert[7]; Matthew B. Goetz[8]; Roger Bedimo[9]; Robert Dubrow[10]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, US; [2]University of Washington School of Medicine, Seattle, WA, US; [3]VA Connecticut Healthcare System and Yale University Schools of Medicine and Public Health, New Haven, CT, US; [4]James J. Peters VA Medical Center, Bronx, NY, US; [5]Atlanta VA Medical Center, Atlanta, GA, US; [6]Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, US; [7]Washington DC Veterans Affairs Medical Center, Washington, DC, US; [8]Los Angeles VA Medical Center, Los Angeles, CA, US; [9]Veterans Affairs North Texas Health Care System, Dallas, TX, US; [10]Yale University School of Public Health, New Haven, CT, US

Session TD-R Themed Discussion — Room 6E

1:30 pm – 2:30 pm

Cryptococcal Meningitis: Host Response, Treatment, and Outcomes

Themed Discussion Leader

Judith A. Aberg, *Icahn School of Medicine at Mount Sinai, New York, NY, US*

834 Local and Systemic Humoral Responses to Cryptococcal Meningitis in Patients With AIDS

Erin E. Finn[1]; Jordan Janoff[1]; Jeremy Rahkola[1]; David B. Meya[2]; Samuel Okurut[2]; Andrew D. Kambugu[2]; Paul Bohjanen[3]; Kirsten Nielsen[3]; David R. Boulware[3]; Edward N. Janoff[1]

[1]Mucosal and Vaccine Research Colorado, Aurora, CO, US; [2]Makerere University College of Health Sciences, Kampala, Uganda; [3]University of Minnesota, Minneapolis, MN, US

835 Antiretroviral Therapy Alters the CSF Immune Response in Cryptococcal Meningitis

James E. Scriven[1]; Britta Urban[1]; Lisa Graham[2]; Charlotte Schutz[2]; Robert J. Wilkinson[3]; David R. Boulware[4]; David Lalloo[1]; Graeme Meintjes[2]

[1]Liverpool School of Tropical Medicine, Liverpool, United Kingdom; [2]University of Cape Town, Cape Town, South Africa; [3]Imperial College London, London, United Kingdom; [4]University of Minnesota, Minneapolis, MN, US

836 Detrimental Outcomes of Unmasking Cryptococcal Meningitis With Recent ART Initiation

Joshua Rhein[1]; Katherine H. Hullsiek[1]; Nathan C. Bahr[1]; Reuben Kiggundu[3]; Darlisha Williams[3]; Henry W. Nabeta[3]; Abdu Musubire[3]; David B. Meya[3]; David R. Boulware[1]

[1]University of Minnesota, Minneapolis, MN, US; [2]University of Minnesota, Minneapolis, MN, US; [3]Makerere University College of Health Sciences, Kampala, Uganda

837 Impact of ART on Mortality in Cryptococcal Meningitis Patients: High-Income Settings

Suzanne M. Ingle[1]; Jose M. Miro[2]; Hansjakob Furrer[4]; Amy Justice[5]; Michael S. Saag[6]; Christian Manzardo[2]; Anna Esteve[7]; Lauren E. Cain[3]; Jonathan A. Sterne[1]; Margaret T. May[1]

[1]University of Bristol, Bristol, United Kingdom; [2]Hospital Clínic–L'Institut D'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain; [3]Harvard School of Public Health, Boston, MA, US; [4]Bern University Hospital and University of Bern, Bern, Switzerland; [5]Yale University School of Medicine, VA Connecticut Healthcare System, New Haven, CT, US; [6]University of Alabama at Birmingham, Birmingham, AL, US; [7]Centre d'Estudis Epidemiològics Sobre ITS/VIH/SIDA de Catalunya, Barcelona, Spain

838 Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis

Joshua Rhein[1]; Katherine H. Hullsiek[1]; Bozena Morawski[1]; Kyle Smith[1]; Ali Al-Hadab[1]; Abdu Musubire[2]; Darlisha Williams[2]; Kristen Nielsen[1]; David B. Meya[2]; David R. Boulware[1]

[1]University of Minnesota, Minneapolis, MN, US; [2]Makerere University College of Health Sciences, Kampala, Uganda

Session TD-W Themed Discussion — Room 6AB

1:30 pm – 2:30 pm

Serosorting and Seroadaptive Behavior: What's Your Position?

Themed Discussion Leader

Andrew E. Grulich, *University of New South Wales, Sydney, NSW, Australia*

1060 Trends in Sexual Behaviors Among Men Who Have Sex With Men in the United States, the Role of Antiretroviral Therapy and Seroadaptive Strategies

Gabriela Paz-Bailey[1]; Maria Mendoza[1]; Binh Le[1]; Charles E. Rose[1]; Teresa Finlayson[1]; Cyprian Wejnert[1]; Henry F. Raymond[2]; Joseph Prejean[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]San Francisco Department of Public Health, San Francisco, CA, US

1061 Changes in Condomless Sex and Serosorting Among MSM After HIV Diagnosis

Christine M. Khosropour[2]; Julia C. Dombrowski[2]; David A. Katz[2]; Matthew R. Golden[2]

[1]University of Washington, Seattle, WA, US; [2]University of Washington, Seattle, WA, US

1062 Serosorting and Sexual Risk Behavior Influenced by Perceived HIV Serostatus Among MSM

Kathleen A. Brady; Jennifer Shinefeld; Catherine Mezzacappa

Philadelphia Department of Public Health, Philadelphia, PA, US

1063 Use of the Seroadaptive Strategies of Sexual Positioning and Serosorting by MSM in Nigeria

Cristina M. Rodriguez-Hart[1]; Hongjie Liu[2]; Ifeanyi K. Orazulike[3]; Sam Zorowitz[4]; Sylvia Adebajo[5]; Lindsay Hughes[6]; Stefan Baral[7]; Merlin L. Robb[6]; William Blattner[1]; Manhattan Charurat[1]

[1]University of Maryland School of Medicine, Baltimore, MD, US; [2]University of Maryland School of Public Health, College Park, MD, US; [3]International Center on Advocacy and Rights to Health, Abuja, Nigeria; [4]Massachusetts General Hospital and Harvard Medical School, Boston, MA, US; [5]Population Council, Abuja, Nigeria; [6]US Military HIV Research Program, Bethesda, MD, US; [7]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

Session TD-Z Themed Discussion — Room 6C

1:30 pm – 2:30 pm

Economic Implications of ART

Themed Discussion Leader

John Blandford, *US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US*

1104 The Lifetime Medical Cost Savings From Preventing HIV in the United States

Bruce R. Schackman[1]; John Fleishman[6]; Amanda Su[2]; Richard Moore[5]; Rochelle Walensky[2]; David Paltiel[3]; Milton Weinstein[4]; Kenneth Freedberg[2]; Kelly Gebo[5]; Elena Losina[2]

[1]Weill Cornell Medical College, New York, NY, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Yale School of Public Health, New Haven, CT, US; [4]Harvard School of Public Health, Boston, MA, US; [5]Johns Hopkins University School of Medicine, Baltimore, MD, US; [6]Agency for Healthcare Research and Quality, Rockville, MD, US

1119 Survival Benefits Attributable to the Brazilian National ART Policy

Paula M. Luz[1]; Michael P. Girouard[2]; Beatriz Grinsztejn[1]; Kenneth Freedberg[2]; Valdilea Veloso[1]; Elena Losina[4]; Claudio Struchiner[1]; Robert Parker[2]; David Paltiel[3]; Rochelle Walensky[2]

[1]Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil; [2]Massachusetts General Hospital, Boston, MA, US; [3]Yale School of Public Health, New Haven, CT, US; [4]Brigham and Women's Hospital, Boston, MA, US

1110 The Cost-Effectiveness of Early ART Initiation in South Africa: A Quasi-Experiment

Jacob Bor[1]; Ellen Moscoe[2]; Natsayi Chimbindi[3]; Kobus Herbst[3]; Kevindra K. Naidu[3]; Frank Tanser[3]; Deenan Pillay[3]; Till Barnighausen[3]

[1]Boston University School of Public Health, Boston, MA, US; [2]Harvard School of Public Health, Boston, MA, US; [3]Wellcome Trust Africa Centre for Health and Population Studies, Somkhele, South Africa

1111 Community-Based Strategies to Strengthen the Continuum of HIV Care Are Cost-Effective

Jennifer A. Smith[1]; Monisha Sharma[2]; Carol Levin[2]; Jared Baeten[2]; Heidi van Rooyen[3]; Connie Celum[2]; Timothy Hallett[1]; Ruanne V. Barnabas[2]

[1]Imperial College London, London, United Kingdom; [2]University of Washington, Seattle, WA, US; [3]Human Sciences Research Council, Sweetwaters, South Africa

1114 Global Fund Cost Projections for Implementing WHO 2013 Guidelines

Obinna Onyekwena; Ade Fakoya; Michael Johnson; Michael Olszak-Olszewski; Mark Dybul

The Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland

Session O-10 Oral Abstracts — Room 6C

4:00 pm – 6:15 pm

New Antiretroviral Agents, Strategies, and HIV Drug Resistance

Moderators

Constance Delaugerre, *Hôpital Saint-Louis, APHP, Université Paris Diderot, Paris, France*

Richard Harrigan, *BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada*

113LB Tenofovir Alafenamide (TAF) in a Single-Tablet Regimen in Initial HIV-1 Therapy

David Wohl[1]; Anton Pozniak[2]; Melanie Thompson[3]; Edwin DeJesus[4]; Daniel Podzamczer[5]; Jean-Michel Molina[6]; Gordon Crofoot[7]; Christian Callebaut[8]; Hal Martin[8]; Scott McCallister[8]

[1]University of North Carolina, Chapel Hill, NC, US; [2]Chelsea and Westminster Hospital, NHS Foundation Trust, London, United Kingdom; [3]AIDS Research Consortium of Atlanta, Atlanta, GA, US; [4]Orlando Immunology Center, Orlando, FL, US; [5]Hospital Universitari de Bellvitge, Barcelona, Spain; [6]Hopital Saint Louis, Paris, France; [7]Gordon Crofoot Research, Houston, TX, US; [8]Gilead Sciences, Inc, Foster City, CA, US; [9]Gilead Sciences, Inc, Foster City, CA, US

114LB Antiviral Activity/Safety of a Second-Generation HIV-1 Maturation Inhibitor

Carey Hwang[1]; Dirk Schürmann[2]; Christian Sobotha[2]; Heather Sevinsky[1]; Palanikumar Ravindran[1]; Hong Xiao[1]; Neelanjana Ray[1]; Mark Krystal[3]; Ira B. Dicker[3]; **Max Lataillade**[3]

[1]Bristol-Myers Squibb, Princeton, NJ, US; [2]Charité Research Organisation GmbH, Berlin, Germany; [3]Bristol-Myers Squibb, Wallingford, CT, US

115LB Early ART and IPT in HIV-Infected African Adults With High CD4 Count (Temprano Trial)

Christine Danel[1]; Raoul Moh[2]; Delphine Gabillard[1]; Anani Badje[4]; Jerome Le Carrou[1]; Gerard M. Kouame[4]; Jean Baptiste Ntakpe[4]; Hervé Ménan[3]; Serge Eholie[2]; Xavier Anglaret[1]
On behalf of the Temprano Study Group

[1]Inserm, Bordeaux, France; [2]Université Felix Houphouet Boigny, Abidjan, Côte d'Ivoire; [3]CHU de Treichville, Abidjan, Côte d'Ivoire; [4]Programme PACCI, Abidjan, Côte d'Ivoire

116 Antiretroviral Drug Screening Provides Key Insights Into HIV Drug Resistance

Iris Chen[1]; Matthew B. Connor[2]; William Clarke[1]; Mark A. Marzinke[1]; Vanessa Cummings[1]; Sheldon D. Fields[3]; Darrell P. Wheeler[4]; Kenneth H. Mayer[5]; Beryl A. Koblin[6]; Susan H. Eshleman[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [3]Florida International University, Miami, FL, US; [4]Loyola University Chicago, Chicago, IL, US; [5]Fenway Health, Boston, MA, US; [6]New York Blood Center, New York, NY, US

117 Untimed Drug Levels and Resistance in Patients Experiencing Low-Level HIV Viremia

Alejandro Gonzalez-Serna; Luke C. Swenson; Adriana Nohpal; Birgit Watson; Kate Auyeung; Julio Montaner; Richard Harrigan

BC Centre for Excellence in HIV/AIDS, Vancouver, Canada

118 Pretreatment HIV Drug Resistance Increases Regimen Switch in Sub-Saharan Africa

Tamara Sonia Boender[1]; Bernice M. Hoenderboom[1]; Kim C. Sigaloff[1]; Maureen Wellington[2]; Margaret Siwale[3]; Cissy M. Kityo[4]; Alani Sulaimon Akanmu[5]; Mariette E. Botes[6]; Tobias F. Rinke de Wit[1]
On behalf of the PASER Study Group

[1]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands; [2]Newlands Clinic, Harare, Zimbabwe; [3]Lusaka Trust Hospital, Lusaka, Zambia; [4]Joint Clinical Research Centre, Kampala, Uganda; [5]Lagos University Teaching Hospital, Lagos, Nigeria; [6]Muelmed Hospital, Pretoria, South Africa

119 Impact of NRTI Cross-Resistance on Second-Line PI + NRTI Therapy Outcomes in Africa

Nicholas Paton[1]; Cissy Kityo[2]; Jennifer Thompson[5]; Leonard Bagenda[2]; James Hakim[6]; Joep van Oosterhout[4]; Andrew D. Kambugu[3]; Anne Hoppe[5]; Sarah Walker[5]
On behalf of the EARNEST Trial Team

[1]National University of Singapore, Singapore, Singapore; [2]Joint Clinical Research Centre, Kampala, Uganda; [3]Infectious Diseases Institute, Kampala, Uganda; [4]University of Malawi, Blantyre, Malawi; [5]MRC Clinical Trials Unit at University College London, London, United Kingdom; [6]University of Zimbabwe Clinical Research Centre, Harare, Zimbabwe

120 Fitness Effects of Drug-Resistant Strains Across the United States HIV-1 Transmission Network

Joel O. Wertheim[1]; Alexandra M. Oster[2]; Neeraja Saduvala[2]; Walid Heneine[2]; Jeffery A. Johnson[2]; William M. Switzer[2]; Angela L. Hernandez[2]; H. Irene Hall[2]

[1]University of California San Diego, San Diego, CA, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

121 Dolutegravir Resistance Requires Multiple Primary Mutations in HIV-1 Integrase

Arne Frantzell; Christos J Petropoulos; **Wei Huang**

Monogram Biosciences, South San Francisco, CA, US

Session S-4 Symposium — Room 613

4:00 pm – 6:00 pm

Making Sense of Sensing: Innate Immunity and HIV Infection

Target audience: This session is directed to clinicians and scientists interested in innate immune defenses against HIV, viral countermeasures, and the relevance of the ongoing arms race between both of these for the pathogenesis and spread of AIDS.

Level of knowledge: It is assumed that participants are familiar with the basics of HIV replication.

Objectives: At the completion of the session, participants will be able to:

- Describe the most current understanding of how the human host senses, responds to, and restricts HIV infection, and how the virus evades or counteracts host defense mechanisms.
- Appreciate the role of innate immunity in the pathogenesis and spread of HIV disease.

Symposium Conveners

Nathaniel Landau, *NYU School of Medicine, New York, NY, US*
Jairam R. Lingappa, *University of Washington, Seattle, WA, US*

122 **Role of Tetherin in the Evolution and Spread of HIV-1**
Daniel Sauter
Ulm University Medical Center, Ulm, Germany

123-A **Innate Sensing of HIV-1 in Macrophages**
Martin R. Jakobsen
Aarhus University, Aarhus C, Denmark

124 **Innate Sensing and Signaling to HIV-1 in Dendritic Cells**
Teunis Geijtenbeek
Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

125 **How HIV-1 Evades DNA Sensors**
Vineet KewalRamani
National Cancer Institute, Frederick, MD, US

Session S-5 Symposium
Room 6D

4:00 pm – 6:00 pm

Advancing HIV Prevention: Lessons from Biology, Medicine, and Public Health Law

Target audience: This session is directed to clinicians, scientists, and policy makers who are interested in developing or implementing HIV prevention programs for maximal benefit.

Level of knowledge: It is assumed that participants are familiar with basic HIV epidemiology and transmission, and the effect of antiretroviral drugs for preexposure prophylaxis and treatment as prevention.

Objectives: At the completion of the session, participants will be able to:

- Determine how new insights into HIV transmission can assist prevention programs.
- Describe the barriers to scale up of test-and-treat approaches and how the law can help (or inhibit) prevention efforts.

Symposium Conveners

Meg C. Doherty, *World Health Organization (WHO), Geneva, Switzerland*
Jeanne M. Marrazzo, *University of Washington, Seattle, WA, US*

126 **The Biology of HIV Transmission: What We Think We Know and How We Know It**
Julie M. Overbaugh
Fred Hutchinson Cancer Research Center, Seattle, WA, US

127 **HIV Phylogenetics: Lessons for HIV Prevention**
Christophe Fraser
Imperial College London, London, United Kingdom

128 **Optimizing ART: Treatment as Prevention in the US: Will It Be Enough?**
Richard A. Elion
Whitman-Walker Health, Washington, DC, US

129 **Criminalizing HIV: Recent Experience in the United States and Africa to Update Laws and Policies to Promote the Public Health**
Jeffrey Crowley
Georgetown University, Washington, DC, US

Session S-6 Symposium — Room 6E

4:00 pm – 6:00 pm

Tuberculosis: Magic Bullets and Moving Targets

Target audience: This session is directed to clinicians and scientists interested in the pathogenesis, clinical manifestations, treatment, and prevention of tuberculosis (TB).

Level of knowledge: It is assumed that participants are familiar with basic TB epidemiology, clinical features, and treatment.

Objectives: At the completion of the session, participants will be able to:

- List new techniques for TB diagnosis.
- Describe new investigational TB treatment options and strategies.
- Describe the unique situation of children and pregnant women infected with TB.

Symposium Conveners

Alison Grant, *London School of Hygiene and Tropical Medicine, London, United Kingdom*
Ilesh V. Jani, *Instituto Nacional de Saúde, Maputo, Mozambique*

130 **Advances in Mycobacterial Diagnostics**
Mark P. Nicol
University of Cape Town, Cape Town, South Africa

131 **New Medications, Innovative Approaches: Accelerate the TB Regimen Development Pipeline**
Michael Hoelscher
University of Munich, Munich, Germany

132 **Tuberculosis in Pregnancy**
Amita Gupta
Johns Hopkins University School of Medicine, Baltimore, MD, US

133 **Tuberculosis in Children**
Anneke C. Hesseling
Stellenbosch University, Cape Town, South Africa

THURSDAY, FEBRUARY 26, 2015

Session PL-1 Plenary — 4AB Auditorium

8:30 am – 9:00 am

Cardiovascular Disease in HIV Patients: An Emerging Paradigm and Call to Action

134 Cardiovascular Disease in HIV Patients: An Emerging Paradigm and Call to Action

Steven Grinspoon

Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

Session PL-2 Plenary — 4AB Auditorium

9:00 am – 9:30 am

The Price of Selling Sex: HIV Among Female Sex Workers—The Context and the Public Health Response

135 The Price of Selling Sex: HIV Among Female Sex Workers—The Context and the Public Health Response

Frances M. Cowan

University College London, London, United Kingdom

Session O-11 Oral Abstracts — Room 6C

10:00 am – 12:15 pm

Cardiovascular, Bone, and Kidney Health

Moderators

Jennifer F. Hoy, *The Alfred Hospital and Monash University, Melbourne, Victoria, Australia*

Edgar T. Overton, *University of Alabama at Birmingham, Birmingham, AL, US*

136 Statin Therapy Reduces Coronary Noncalcified Plaque Volume in HIV Patients: A Randomized Controlled Trial

Janet Lo[1]; Michael Lu[2]; Ezinne Ihenachor[1]; Jeffrey Wei[1]; Sara Looby[1]; Kathleen Fitch[1]; Suhny Abbara[2]; Gregory Robbins[1]; Udo Hoffmann[2]; Steven Grinspoon[1]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]Massachusetts General Hospital, Boston, MA, US

137 Rosuvastatin Arrests Progression of Carotid Intima-Media Thickness in Treated HIV

Chris T. Longenecker[1]; Ying Jiang[1]; Sara M. Debanne[1]; Danielle Labbato[2]; Bruce Kinley[2]; Norma Storer[2]; **Grace A. McComsey**[1]

[1]Case Western Reserve University, Cleveland, OH, US; [2]University Hospitals of Cleveland, Cleveland, OH, US

138 Calcified Plaque Burden Is Associated With Serum Gut Microbiota-Generated TMA in HIV

Suman Srinivasa[1]; Kathleen V. Fitch[1]; Janet Lo[1]; Hanane Kadar[2]; Kimberly Wong[1]; Suhny Abbara[3]; Dominique Gauguier[2]; Jacqueline Capeau[2]; Franck Boccara[2]; Steven K. Grinspoon[1]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]University Pierre & Marie Curie, Paris, France; [3]University of Texas Southwestern Medical Center, Dallas, TX, US

139 Varenicline vs Placebo for Smoking Cessation: ANRS 144 Inter-ACTIV Randomized Trial

Patrick Mercie[3]; Caroline Roussillon[1]; Christine Katlama[4]; Aurélie Beuscart[1]; Samuel Ferret[2]; Nathalie Wirth[5]; David Zucman[6]; Xavier Duval[7]; Genevieve Chene[1]
On behalf of the ANRS 144 inter-ACTIV study group

[1]Inserm U897, Bordeaux, France; [2]Hosp. Saint-Louis, Paris, France; [3]Hosp. Saint-André, Bordeaux, France; [4]Hosp. La Pitié-Salpêtrière, Paris, France; [5]Hosp. De Brabois, Vandoeuvre les Nancy, France; [6]Hosp. Foch, Suresnes, France; [7]CIC 1425, Paris, France

140 Body Composition Changes After Initiation of Raltegravir or Protease Inhibitors

Grace A. McComsey[1]; Carlee Moser[2]; Judith S. Currier[8]; Heather Ribaudo[2]; Pawel Paczuski[2]; Michael P. Dube[5]; Robert L. Murphy[6]; Jennifer Rothenberg[7]; James H. Stein[4]; Todd T. Brown[3]

[1]Case Western Reserve University, Cleveland, OH, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]University of Wisconsin School of Medicine and Public Health, Madison, WI, US; [5]University of Southern California, Los Angeles, CA, US; [6]Northwestern University, Chicago, IL, US; [7]Social & Scientific Systems, Inc., Silver Spring, MD, US; [8]University of California Los Angeles, Los Angeles, CA, US

141 Fracture Prediction With Modified FRAX in Older HIV+ and HIV- Men

Michael T. Yin[1]; Melissa Skanderson[7]; Stephanie Shiau[1]; Katherine Harwood[1]; Josh Aschheim[3]; David Rimland[2]; Cynthia Gibert[5]; Maria Rodriguez-Barradas[4]; Roger Bedimo[6]; Julie Womack[7]

[1]Columbia University Medical Center, New York, NY, US; [2]VAMC and Emory School of Medicine, Atlanta, GA, US; [3]Arcadia Healthcare Solutions, New York, NY, US; [4]Baylor College of Medicine, Houston, TX, US; [5]VA Medical Center, George Washington University, Washington, DC, US; [6]University of Texas, Dallas, TX, US; [7]VA Connecticut Healthcare System, West Haven, CT, US

142 Exposure to Antiretrovirals (ARVs) and Development of Chronic Kidney Disease (CKD)

Amanda Mocroft[1]; Jens D. Lundgren[2]; Michael Ross[3]; Christoph Fux[4]; Peter Reiss[5]; Olivier Moranne[6]; Philippe Morlat[7]; Antonella d'Arminio Monforte[8]; Ole Kirk[2]; Lene Ryom[2]
On behalf of the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group

[1]University College London, London, United Kingdom; [2]Copenhagen HIV Programme, Centre for Health and Infectious Diseases Network, University of Copenhagen, Denmark, Denmark; [3]Division of Nephrology, Mount Sinai School of Medicine, New York, NY, US; [4]Clinic for Infectious Diseases and Hospital Hygiene, Kantonsspital Aarau, Aarau, Switzerland; [5]Academic Medical Center, Div. of Infectious Diseases and Dept. of Global Health, University of Amsterdam, Amsterdam, Netherlands; [6]Université de Bordeaux, Inserm U 897, Bordeaux, France; [7]Public Health Department, Nice, France; [8]Istituto Di Clinica Malattie Infettive e Tropicale, Milan, Italy

143LB Renal and Bone Safety of Tenofovir Alafenamide vs Tenofovir Disoproxil Fumarate

Paul E. Sax[7]; Michael S. Saag[2]; Michael T. Yin[3]; Frank A. Post[4]; Shinichi Oka[8]; Ellen Koenig[5]; Benoit Trottier[9]; Jaime Andrade-Villanueva[6]; Huyen Cao[1]; Marshall W. Fordyce[1]

[1]Gilead Sciences Inc, Foster City, CA, US; [2]University of Alabama at Birmingham, Birmingham, AL, US; [3]College of Physicians and Surgeons, Columbia University, New York, NY, US; [4]King's College Hospital, London, United Kingdom; [5]Dominican Institute for Virologic Studies, Santo Domingo, Dominican Republic; [6]Unidad de VIH del Hospital Civil de Guadalajara, Guadalajara, Mexico; [7]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, US; [8]National Center for Global Health and Medicine, Japan, Tokyo, Japan; [9]Clinique Medicale l'Actuel, Montreal, Canada

144 Special Presentation: Update on National Heart, Lung, and Blood Institute High-Impact AIDS Research

Monica Shah

National Heart, Lung, and Blood Institute, Bethesda, MD, US

Session O-12 Oral Abstracts — Room 6AB

10:00 am – 12:00 pm

Curing HCV: Mission Accomplished

Moderators

Karine Lacombe, *Saint Antoine Hospital, AP-HP, Paris, France*

John W. Ward, *Centers for Disease Control and Prevention, Atlanta, GA, US*

145 The Burden of Liver Disease Among Persons With Hepatitis C in the United States

Monina Klevens[1]; Xiaohua Huang[2]; Anthony E. Yeo[2]; Mouneer Odeh[2]; Rick L. Pesano[2]; John W. Ward[1]

[1]US Centers for Disease Control and Prevention, Atlanta, GA, US; [2]Quest Diagnostics, Madison, NJ, US

146 High Efficacy of Daclatasvir/Asunaprevir/PR in HIV/HCV1-4 Null Responders (ANRS HC30)

Lionel Piroth[1]; Hubert Paniez[2]; Corine Vincent[2]; Karine Lacombe[3]; David Rey[4]; Didier Neau[5]; Jacques Izopet[6]; Alpha Diallo[7]; Laurence Meyer[2]; Jean-Michel Molina[8]

[1]CHU Dijon, Dijon, France; [2]Inserm, Paris, France; [3]Hôpital Saint-Antoine, Paris, France; [4]Strasbourg University Hospital, Strasbourg, France; [5]CHU, Bordeaux, France; [6]CHU, Toulouse, France; [7]Inserm-ANRS, Paris, France; [8]CHU Saint Louis, Paris, France

147 High SVR Regardless of Time to Suppression With ABT-450/r/Ombitasvir and Dasabuvir+RBV

David Wyles[1]; Joseph J. Eron[2]; Roger Trinh[3]; Jay Lalezari[4]; Chia Wang[5]; Laveeza Bhatti[6]; Peter Gulick[7]; Barbara McGovern[3]; Linda Fredrick[3]; Mark Sulkowski[8]

[1]University of California San Diego, La Jolla, CA, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]Abbvie Inc, North Chicago, IL, US; [4]Quest Clinical Research, San Francisco, CA, US; [5]Virginia Mason Medical Center, Seattle, WA, US; [6]AIDS Healthcare Foundation, Los Angeles, CA, US; [7]Michigan State University, East Lansing, MI, US; [8]Johns Hopkins University, Baltimore, MD, US

148 The Paradox of Highly Effective Sofosbuvir Combo Therapy Despite Slow Viral Decline

Thi Huyen Tram Nguyen[1]; **Jérémie Guedj**[1]; Laetitia Canini[2]; Anu Osinusi[5]; Phillip S. Pang[5]; John McHutchison[5]; Henry Masur[6]; Anita Kohli[3]; Shyam Kottilil[4]; Alan S Perelson[2]

[1]IAME, UMR 1137, Inserm, F-75018 Paris, France; Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France, Paris, France; [2]Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, NM, US; [3]Clinical Research Directorate/Clinical Monitoring Research Program, Leidos Biomedical Research, Inc, Frederick National Laboratory for Cancer Research, Frederick, MD, US; [4]Laboratory of Immunoregulation, NIAID, NIH, Bethesda, MD, US; [5]Gilead Sciences, Inc, Foster City, MD, US; [6]NIH Clinical Center, Bethesda, MD, US

149 Real-World Pharmaceutical Costs in the Simeprevir/Sofosbuvir Era: $164,485 per SVR4

Kian Bichoupan[1]; Neeta Tandon[2]; Rachana Yalamanchili[1]; Neal M. Patel[1]; Sweta Chekuri[1]; Alyson Harty[1]; Thomas Schiano[1]; Ponni V. Perumalswami[1]; Douglas Dieterich[1]; Andrea D. Branch[1]

[1]Mount Sinai School of Medicine, New York, NY, US; [2]Janssen Scientific Affairs, Titusville, NJ, US

150 Impact of Deferring HCV Treatment on Liver-Related Events in HIV+ Patients

Cindy Zahnd[1]; Luisa P. Salazar-Vizcaya[1]; Jean-François Dufour[2]; Beat Müllhaupt[3]; Gilles Wandeler[1]; Roger Kouyos[3]; Barbara Bertisch[1]; Andri Rauch[2]; Olivia Keiser[1]
On behalf of the Swiss HIV and Hepatitis C Cohort Studies

[1]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland; [2]University Hospital Bern, Bern, Switzerland; [3]University Hospital Zurich, Zurich, Switzerland

151LB Daclatasvir in Combination With Sofosbuvir for HIV/HCV Coinfection: ALLY-2 Study

David Wyles[1]; Peter Ruane[2]; Mark Sulkowski[3]; Douglas Dieterich[4]; Anne Luetkemeyer[5]; Timothy Morgan[6]; Kenneth E. Sherman[7]; Zhaohui Liu[8]; Stephanie Noviello[8]; Peter Ackerman[8]

[1]University of California San Diego, La Jolla, CA, US; [2]Ruane Medical and Liver Health Institute, Los Angeles, CA, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]Icahn School of Medicine at Mount Sinai, New York, NY, US; [5]University of California and San Francisco General Hospital, San Francisco, CA, US; [6]VA Long Beach Healthcare System, Long Beach, CA, US; [7]University of Cincinnati College of Medicine, Cincinnati, OH, US; [8]Bristol-Myers Squibb Co, Princeton, NJ, US

152LB Ledipasvir/Sofosbuvir for 12 Weeks in Patients Coinfected With HCV and HIV-1

Susanna Naggie[1]; Curtis Cooper[2]; Michael S. Saag[3]; Jenny C. Yang[4]; Luisa M. Stamm[4]; Phillip S. Pang[4]; John McHutchison[4]; Douglas Dieterich[5]; Mark Sulkowski[6]
On behalf of the ION-4 Study Team

[1]Duke Clinical Research Institute, Durham, NC, US; [2]University of Ottawa, Ottawa, Canada; [3]University of Alabama at Birmingham, Birmingham, AL, US; [4]Gilead Sciences, Inc, Foster City, CA, US; [5]Mount Sinai Health System, New York, NY, US; [6]Johns Hopkins University School of Medicine, Baltimore, MD, US

Session O-13 Oral Abstracts — Room 6D

10:00 am – 12:15 pm

Reaching Populations: Demonstrating Impact

Moderators

Sarah Fidler, *Imperial College and Imperial College NHS Trust, London, United Kingdom*

Jessica E. Justman, *Columbia University Medical Center, New York, NY, US*

153 Population Viral Load in Three High HIV Prevalence Settings in Sub-Saharan Africa

David Maman[1]; Helena Huerga[1]; Gilles Van Cutsem[2]; Irene Mukui[3]; Benson Chilima[4]; Beatrice Kirubi[5]; Ruggero G. Giuliani[2]; Elisabeth Szumilin[6]; Charles Masiku[7]; Jean-François Etard[1]

[1]Epicentre/Médecins Sans Frontières, Paris, France; [2]Médecins Sans Frontières, Cape Town, South Africa; [3]National AIDS and STDs Control Program, Nairobi, Kenya; [4]Ministry of Health, Lilongwe, Malawi; [5]Médecins Sans Frontières, Nairobi, Kenya; [6]Médecins Sans Frontières, Paris, France; [7]Médecins Sans Frontières, Lilongwe, Malawi

154 Disparities in Engagement Within HIV Care in South Africa

Simbarashe Takuva[1]; Alison Brown[2]; William Macleod[3]; Yogan Pillay[4]; Valerie Delpech[2]; Adrian J. Puren[1]

[1]National Institute for Communicable Diseases, NHLS, Johannesburg, South Africa; [2]Centre for Infectious Diseases Surveillance, Public Health England, London, United Kingdom; [3]Boston University, Boston, MA, US; [4]National Department of Health, Pretoria, South Africa

155 Decentralizing Access to Antiretroviral Therapy Services for Adults in Swaziland

Andrew F. Auld[1]; Harrison Kamiru[2]; Charles Azih[3]; Andrew L. Baughman[1]; Harriet Nuwagaba-Biribonwoha[2]; Peter Ehrenkranz[1]; Simon Agolory[1]; Tedd V. Ellerbrock[1]; Velephi Okello[3]; George Bicego[1]

[1]US Centers for Disease Control and Prevention, Atlanta, GA, US; [2]ICAP, Columbia University, New York, NY, US; [3]Ministry of Health, Mbabane, Swaziland

156 Who Are the 10-Year AIDS Survivors on Antiretroviral Therapy in Haiti?

Samuel Pierre[1]; Ashita Batavia[2]; Patrice Severe[1]; Vanessa Rouzier[1]; Benedict Charles[1]; Jean Pape[1]; Warren Johnson[2]; Daniel Fitzgerald[2]; Margaret L. McNairy[2]
On behalf of Les Centres GHESKIO CTU

[1]Les Centres GHESKIO, Port-au-Prince, Haiti; [2]Weill Cornell Medical College, New York, NY, US

157 Nationwide Evaluation of Antiretroviral Therapy Coverage on Prevention in Rwanda: A Multisectional Time-Trend Analysis

Sabin Nsanzimana[2]; Eric Remera[2]; Steve Kanters[1]; Eric Dusabe[2]; Adeline Dukuze[2]; Till Barnighausen[3]; Eran Bendavid[1]; Julio Montaner[4]; **Edward Mills**[1]
On behalf of the Rwanda Treatment as Prevention Working Group

[1]Stanford University, Vancouver, Canada; [2]Rwanda Biomedical Centre, Kigali, Rwanda; [3]Harvard School of Public Health, Boston, MA, US; [4]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada

158 Impact of Male Circumcision Scale-Up on Community-Level HIV Incidence in Rakai, Uganda

Xiangrong Kong[1]; Godfrey Kigozi[2]; Fred Nalugoda[2]; David Serwadda[3]; Maria J. Wawer[1]; Ronald H. Gray[1]
On behalf of the Rakai Health Sciences Program

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]Rakai Health Sciences Program, Entebbe, Uganda; [3]Makerere University College of Health Sciences, Kampala, Uganda

159 Effects of Antiretroviral Treatment on Health Care Utilization in Rural South Africa

Jan A. Hontelez[1]; Frank Tanser[2]; Sake J. de Vlas[1]; Kevindra K. Naidu[2]; Rob Baltussen[3]; Deenan Pillay[2]; Till Barnighausen[2]

[1]Erasmus University Medical Center, Nijmegen, Netherlands; [2]Africa Centre for Health and Population Studies, Somkhele, South Africa; [3]Radboud University Medical Centre, Nijmegen, Netherlands

160 The Impact of PEPFAR Abstinence and Faithfulness Funding Upon HIV Risk Behaviors in Sub-Saharan Africa

Nathan C. Lo; Anita Lowe; Eran Bendavid

Stanford University School of Medicine, Stanford, CA, US

161 The Impact of Antiretroviral Therapy on Adult Life Expectancy in Sub-Saharan Africa

Georges Reniers[8]; Jeffrey Eaton[1]; Jessica Nakiyingi-Miiro[2]; Amelia C. Crampin[4]; Chodziwadziwa Kabudula[5]; Kobus Herbst[3]; Mark Urassa[6]; Amek Nyaguara[7]; Emma Slaymaker[8]
On behalf of the ALPHA Network

[1]Imperial College London, London, United Kingdom; [2]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda; [3]Africa Centre for Health and Population Studies, Mtubatuba, South Africa; [4]Karonga Prevention Study, Chilumba, Malawi; [5]University of the Witwatersrand, Johannesburg, South Africa; [6]National Institute for Medical Research, Mwanza, United Republic of Tanzania; [7]Kenya Medical Research Institute-Centers for Disease Control, Kisumu, Kenya; [8]London School of Hygiene and Tropical Medicine, London, United Kingdom

Session O-14 Oral Abstracts — Room 613

10:00 am – 12:15 pm

Immune Mechanisms: The Road to Protection

Moderators

Katharine J. Bar, *University of Pennsylvania, Philadelphia, PA, US*

Bruce Walker, *Ragon Institute of MIT, MGH and Harvard, Cambridge, MA, US*

162 Passively Acquired ADCC Activity in HIV-Infected Infants Correlates With Survival

Caitlin Milligan[1]; Barbra A. Richardson[1]; Grace John-Stewart[2]; Ruth W. Nduati[3]; Julie M. Overbaugh[1]

[1]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [2]University of Washington, Seattle, WA, US; [3]University of Nairobi, Nairobi, Kenya

163 AAV-Expressed eCD4-Ig Protects Rhesus Macaques From Multiple SHIV-AD8 Challenges

Michael Farzan

The Scripps Research Institute, Jupiter, FL, US

164LB HIV Neutralizing Antibodies Induced by Native-Like Envelope Trimers

Rogier Sanders
The WCMC/Scripps/AMC HIVRAD team

Academic Medical Center University of Amsterdam, Amsterdam, Netherlands

165 Efficacy Loss of BnAbs During HIV-1 Cell-Cell Spread Is Strain- and Epitope-Dependent

Lucia Reh; Carsten Magnus; Merle Schanz; Jacqueline Weber; Therese Uhr; Peter Rusert; Alexandra Trkola

University of Zurich, Zurich, Switzerland

166 Peripheral T Follicular Helper Cells With Universal Helper Activity in HIV Infection

Bruce Schultz; Alexander Oster; Franco Pissani; Jeffrey E. Teigler; Michael A. Eller; Merlin L. Robb; Jerome H. Kim; Nelson L. Michael; Diane Bolton; **Hendrik Streeck**

US Military HIV Research Program, Silver Spring, MD, US

167 Redirected Killing of HIV-Infected T Cells by Germinal Center CD8 T Cells

Constantinos Petrovas[1]; Sara Ferrando-Martinez[1]; Michael Gerner[2]; Amarendra Pegu[1]; Perla Del Río-Estrada[3]; Kristin Boswell[1]; Manuel Leal[4]; Gustavo Reyes-Teran[3]; Ronald Germain[2]; Richard A. Koup[1]

[1]Vaccine Research Center, National Institute of Allergy and Infectious Diseases, Bethesda, MD, US; [2]NIAID-NIH, Bethesda, MD, US; [3]Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico; [4]Instituto de Biomedicina de Sevilla, Sevilla, Spain

168 IL-21 Reduces Inflammation and Virus Persistence in ART-Treated SIV-Infected Macaques

Luca Micci[1]; Emily Ryan[1]; Colleen McGary[1]; Sara Paganini[1]; Guido Silvestri[1]; Mike Piatak[2]; Jeffrey Lifson[2]; Francois Villinger[1]; Jason M. Brenchley[3]; Mirko Paiardini[1]

[1]Yerkes National Primate Research Center, Emory University, Atlanta, GA, US; [2]Leidos Biomedical Research, Inc, Frederick, MD, US; [3]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

169 Discovery of CD8$^+$ T Cell Epitopes Encoded by the HIV 5′ Leader Sequence

Edward Kreider[1]; Katja J. Pfafferott[2]; Thomas Partridge[2]; Hui Li[1]; Ranjit Warrier[1]; Benedikt M. Kessler[2]; Andrew J. McMichael[2]; Persephone Borrow[2]; Beatrice H. Hahn[1]; George M. Shaw[1]

[1]University of Pennsylvania, Philadelphia, PA, US; [2]University of Oxford, Headington, United Kingdom

170LB Neutralizing Antibodies Differ Between HIV-1–Infected RV144 Vaccinees and Placebos

Shelly J. Krebs[1]; Morgane Rolland[1]; Sodsai Tovanabutra[1]; Ivelin Georgiev[2]; Agnes-Laurence Chenine[1]; Victoria R. Polonis[1]; Supachai Rerks-Ngarm[3]; Peter D. Kwong[2]; Nelson L. Michael[1]; Jerome H. Kim[1]
On behalf of the RV152 Study Group

[1]US Military HIV Research Program, Silver Spring, MD, US; [2]Vaccine Research Center, NIAID, NIH, Bethesda, MD, US; [3]Ministry of Public Health, Bangkok, Thailand

Session TD-M Themed Discussion — Room 615

1:30 pm – 2:30 pm

Identifying Recent Infections: Issues of False Recency

Themed Discussion Leader

Michael Busch, *Blood Systems Research Institute, San Francisco, CA, US*

612 A Generalized Entropy Measure of Viral Diversity for Identifying Recent HIV-1 Infections

Julia W. Wu; Oscar Patterson-Lomba; Marcello Pagano

Harvard School of Public Health, Boston, MA, US

626 Viral Load is Critical in Limiting False-Recent Results From HIV Incidence Assays

Reshma Kassanjee[1]; Shelley Facente[2]; Sheila Keating[3]; Elaine McKinney[4]; Kara Marson[2]; Christopher D. Pilcher[2]; Michael Busch[3]; Gary Murphy[4]; **Alex Welte**[1]
On behalf of the Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA)

[1]South African DST/NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), University of Stellenbosch, Stellenbosch, South Africa; [2]University of California San Francisco, San Francisco, CA, US; [3]Blood Systems Research Institute, San Francisco, CA, US; [4]Public Health England, London, United Kingdom

625 False Recent Rates for Two Recent Infection Testing Algorithms, South Nyanza, Kenya

Clement Zeh[1]; David Maman[4]; Harrison Omondi[2]; Alex Morwabe[2]; Collins Odhiambo[2]; Beatrice Kirubi[4]; Irene Mukui[3]; Martinus W. Borgdorff[1]; Jean-François Etard[4]; Andrea A. Kim[1]

[1]US Centers for Disease Control and Prevention, Kisumu, Kenya; [2]Kenya Medical Research Institute, Kisumu, Kenya; [3]National AIDS and STI Control and Prevention, Nairobi, Kenya; [4]Médecins Sans Frontières, Paris, France

622 The Effect of HIV-1 Subtype A, C and D on Cross-Sectional Incidence Assay Performance

Andrew F. Longosz[2]; Mary Grabowski[2]; Charles S. Morrison[3]; Ronald H. Gray[2]; Connie Celum[4]; Quarraisha Abdool Karim[5]; Hilmarie Brand[6]; Thomas C. Quinn[1]; Susan H. Eshleman[2]; **Oliver B. Laeyendecker**[1]

[1]National Institute of Allergy and Infectious Diseases, Baltimore, MD, US; [2]Johns Hopkins University, Baltimore, MD, US; [3]FHI 360, Durham, NC, US; [4]University of Washington, Seattle, WA, US; [5]CAPRISA, University of KwaZulu-Natal, Congella, South Africa; [6]SACEMA, Stellenbosch University, Stellenbosch, South Africa

Session TD-N Themed Discussion — Room 6AB

1:30 pm – 2:30 pm

Next-Generation HCV Therapeutics: From Clinical Trials to the Clinic

Themed Discussion Leader

Debika Bhattacharya, *University of California Los Angeles CARE Center, Los Angeles, CA, US*

646 German Cohort on Sofosbuvir-Based Therapy for HIV/HCV and HCV Infection (GECOSO)

Stefan Christensen[2]; Ingiliz Patrick[3]; Dietrich Hueppe[7]; Thomas Lutz[4]; Karl Georg Simon[6]; Knud Schewe[5]; Heiner Busch[2]; Axel Baumgarten[3]; Guenther Schmutz[1]; **Stefan Mauss**[1]

[1]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; [2]CIM Infectious Diseases, Muenster, Germany; [3]Medizinisches Infektiologie Zentrum Berlin, Berlin, Germany; [4]Infektiologikum, Frankfurt, Germany; [5]Infektionsmedizinisches Centrum Hamburg, Hamburg, Germany; [6]Practice for Gastroenterology Leverkusen, Leverkusen, Germany; [7]Practice for Gastroenterology Herne, Herne, Germany

649 Successful HCV Treatment With Direct Acting Antivirals in HIV/HCV Patients

Jennifer L. Grant[1]; Valentina Stosor[1]; Frank J. Palella[1]; Richard M. Green[1]; Guajira Thomas[1]; Donna V. McGregor[1]; Milena M. McLaughlin[2]; Sudhir Penugonda[1]; Michael Angarone[1]; **Claudia Hawkins**[1]

[1]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [2]Midwestern University, Chicago, IL, US

645 Effectiveness of Sofosbuvir/Simeprevir for HIV/HCV Patients in Clinical Practice

Jody Gilmore[1]; Kenneth Lynn[1]; Delisha Breen[1]; Stacey Trooskin[2]; Jihad Slim[3]; Nancy Scangarello[3]; Alvin Kingcade[4]; Katie Hunyh[4]; Vincent Lo Re[1]; **Jay R. Kostman**[1]

[1]Perelman School of Medicine, Philadelphia, PA, US; [2]Drexel University College of Medicine, Philadelphia, PA, US; [3]St Michael's Medical Center, Newark, NJ, US; [4]Philadelphia Health Management Corporation, Philadelphia, PA, US

648 Simeprevir and Sofosbuvir Regimens for Hepatitis C: Decompensation and Serious AEs

Ponni V. Perumalswami[1]; Kian Bichoupan[1]; Lawrence Ku[1]; Neal M. Patel[1]; Rachana Yalamanchili[1]; Thomas Schiano[1]; Mark Woodward[2]; Douglas Dieterich[1]; Andrea D. Branch[1]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, US; [2]George Institute for Health at the University of Oxford, Oxford, United Kingdom

651 Majority of HIV/HCV Patients Need to Switch ART to Accommodate Simeprevir

Rebecca Cope[1]; Aaron Pickering[2]; Thomas Glowa[1]; Samantha Faulds[1]; Peter Veldkamp[1]; **Ramakrishna Prasad**[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]University of Maryland, Glen Burnie, MD, US

644 Sofosubuvir, Simeprevir, +/- Ribavirin in HCV Protease Inhibitor-Experienced Patients

Kristen M. Marks; Ethan M. Weinberg; Sonal Kumar; Carrie Down; Ype P. de Jong; Leah A. Burke; Mary C. Olson; Ira M. Jacobson

Weill Cornell Medical College, New York, NY, US

Session TD-P Themed Discussion — Room 6E

1:30 pm – 2:30 pm

Cardiovascular Risk Prediction: Can We Do Better?

Themed Discussion Leader

Nina Friis-Moller, *Odense University Hospital, Odense, Denmark*

746 Cumulative HIV Care Measures Highly Associated With Acute Myocardial Infarction

Jorge L. Salinas[1]; Christopher T. Rentsch[2]; Vincent C. Marconi[1]; Janet Tate[3]; Adeel A. Butt[4]; Matthew S. Freiberg[4]; Matthew B. Goetz[5]; Maria Rodriguez-Barradas[6]; Amy Justice[3]; David Rimland[1]

[1]Emory University, Atlanta, GA, US; [2]Atlanta VA Hospital, Decatur, GA, US; [3]Yale University, New Haven, CT, US; [4]University of Pittsburgh, Pittsburgh, PA, US; [5]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US; [6]Baylor College of Medicine, Houston, TX, US

747 Cardiovascular Disease Risk Prediction in the HIV Outpatient Study (HOPS)

Angela M. Thompson-Paul[1]; **Kenneth A. Lichtenstein**[2]; Carl Armon[3]; Kate Buchacz[1]; Rachel Debes[3]; Joan S. Chmiel[4]; Frank J. Palella[4]; Stanley C. Wei[1]; Jacek Skarbinski[1]; John T. Brooks[1]

[1]US Centers for Disease Control and Prevention, Atlanta, GA, US; [2]National Jewish Health, Denver, CO, US; [3]Cerner Corporation, Vienna, VA, US; [4]Northwestern University, Feinberg School of Medicine, Chicago, IL, US

748 Incidence and Risk of Myocardial Infarction (MI) by Type in the NA-ACCORD

Daniel R. Drozd[1]; Mari M. Kitahata[1]; Keri N. Althoff[2]; Jinbing Zhang[2]; Susan R. Heckbert[1]; Matthew J. Budoff[3]; Frank J. Palella[4]; Daniel B. Klein[5]; Richard D. Moore[6]; Heidi M. Crane[1]

[1]University of Washington, Seattle, WA, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]University of California Los Angeles, Los Angeles, CA, US; [4]Northwestern University, Chicago, IL, US; [5]Kaiser Permanente Northern California, Hayward, CA, US; [6]Johns Hopkins University, Baltimore, MD, US

750 HIV-Infected Veterans and the New ACC/AHA Cholesterol Guidelines: Got Statins?

Meredith E. Clement[1]; Lawrence Park[1]; Ann Marie Navar-Boggan[1]; Nwora L. Okeke[1]; Michael Pencina[1]; Pamela Douglas[1]; Susanna Naggie[1]

[1]Duke University, Durham, NC, US; [2]Duke University, Durham, NC, US; [3]Duke University, Durham, NC, US

751 Evaluation of the ACC/AHA CVD Risk Prediction Algorithm Among HIV-Infected Patients

Susan Regan[2]; James B. Meigs[2]; Joseph Massaro[3]; Ralph B. D'Agostino[3]; Steven Grinspoon[2]; **Virginia A. Triant**[2]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Boston University, Boston, MA, US; [4]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

Session TD-T Themed Discussion — Room 6D

1:30 pm – 2:30 pm

Keys to the Kingdom: Viral Suppression in Pregnant and Postpartum Women

Themed Discussion Leader

Laurent Mandelbrot, *Hopital Louis Mourier, Colombes, France*

863 Specific Effects of ZDV, 3TC and LPV/r on HIV-1 RNA Viral Load During Pregnancy

Patumrat Sripan[1]; Sophie Le Coeur[5]; Lily Ingsrisawang[2]; Tim R. Cressey[3]; Jean-Marc Tréluyer[6]; Naïm Bouazza[4]; Frantz Foissac[4]; Gonzague Jourdain[3]; Marc G. Lallemant[3]; Saïk Urien[7]

[1]ED420, University of Paris Sud 11, Paris Descartes, Paris, France/PHPT-IRD UMI 174, Chiang Mai, Thailand/Department of Statistics, Faculty of Science, Kasetsart University, Bangkok, Thailand; [2]Department of Statistics, Faculty of Science, Kasetsart University, Bangkok, Thailand; [3]PHPT-IRD UMI 174, Faculty of Associated Medical Sciences, Chiang Mai University/ Harvard School of Public Health, Chiang Mai, Thailand; [4]EA 08 Université Paris Descartes, Sorbonne Paris Cité, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, Paris, France; [5]Institut d'Etudes Démographiques, Institut de Recherche Pour le Développement (UMR 196 CEPED), Paris, France/Harvard School of Public Health, Boston, MA, USA/Faculty of Associated Medical Science, Chiang Mai University, Chiang Mai, Thailand; [6]EA 08 Université Paris Descartes, Sorbonne Paris Cité, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, Service de Pharmacologie Clinique, AP-HP, Groupe Hospitalier Paris Centre, CIC-0901 Inserm, Cochin-Necker, Paris, France; [7]EA 08 Université Paris Descartes, Sorbonne Paris Cité, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, CIC-0901 Inserm, Cochin-Necker, Paris, France

864 Viral Suppression After Antiretroviral Therapy Initiation in Pregnancy in South Africa

Landon Myer[1]; Tamsin Phillips[1]; Nei-Yuan Hsiao[2]; Allison Zerbe[3]; Jo Ramjith[1]; Linda-Gail Bekker[1]; James A. McIntyre[4]; Elaine J. Abrams[3]

[1]University of Cape Town, Cape Town, South Africa; [2]National Health Laboratory Services/ University of Cape Town, Cape Town, South Africa; [3]ICAP at Columbia University, New York, NY, US; [4]Anova Health Institute, Johannesburg, South Africa

865 Maternal Viral Load in the Context of PMTCT B+ Within the Kabeho Study in Kigali

Emily A. Bobrow[1]; Placidie Mugwaneza[2]; Gilles F. Ndayisaba[3]; Dieudonne Ndatimana[3]; **Michelle Gill**[1]; Heather J. Hoffman[4]; Cyprien Baribwira[5]; Laura Guay[1]; Anita Asiimwe[6]
On behalf of the Kabeho Study Team

[1]Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, US; [2]Ministry of Health, Kigali, Rwanda; [3]Elizabeth Glaser Pediatric AIDS Foundation, Kigali, Rwanda; [4]George Washington University Milken Institute School of Public Health, Washington, DC, US; [5]University of Maryland, School of Medicine, Kigali, Rwanda; [6]Rwanda University Teaching Hospitals, Kigali, Rwanda

866 ART Response Among Pregnant and Postpartum Women With Acute Versus Chronic HIV-1

Alison L. Drake[1]; John Kinuthia[2]; Daniel Matemo[2]; Barbra Richardson[1]; Michael Chung[1]; James N. Kiarie[2]; Sandy Emery[3]; Julie M. Overbaugh[3]; Grace John-Stewart[1]

[1]University of Washington, Seattle, WA, US; [2]University of Nairobi, Nairobi, Kenya; [3]Fred Hutchinson Cancer Research Center, Seattle, WA, US

Session TD-V Themed Discussion — Room 6C

1:30 pm – 2:30 pm

PEP: Remember Me?

Themed Discussion Leader

Kenneth H. Mayer, *Fenway Health, Boston, MA, US*

959 Tenofovir/Emtricitabine Plus LPV/r vs MVC or Raltegravir for PEP: 2 Randomized Trials

Lorna Leal; Agathe Leon; Berta Torres; Alexy Inciarte; Constanza Lucero; Josep Mallolas; Maria Martinez-Rebollar; Ana González-Cordón; Jose M. Gatell; Felipe Garcia

Hospital Clínic Barcelona, Barcelona, Spain

958 Rilpivirine-Emtricitabine-Tenofovir for HIV Nonoccupational Postexposure Prophylaxis

Rosalind Foster[1]; John McAllister[2]; Tim R. Read[3]; Anna Pierce[4]; Robyn Richardson[2]; Anna McNulty[1]; Andrew Carr[2]
On behalf of the EPEP Study Researchers

[1]Sydney Sexual Health Centre, Sydney, Australia; [2]St Vincent's Centre for Applied Medical Research, Sydney, Australia; [3]Melbourne Sexual Health Centre, Melbourne, Australia; [4]The Alfred Hospital, Melbourne, Australia

957 Significant Intolerability of Efavirenz in HIV Occupational Postexposure Prophylaxis

Surasak Wiboonchutikul[1]; Varaporn Thientong[1]; Patama Sutha[1]; Boonchai Kowadisaiburana[2]; Weerawat Manosuthi[1]

[1]Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand; [2]Bangkok Hospital, Bangkok, Thailand

961 Management of Acute HIV After Initiation of Postexposure Prophylaxis: Challenges and Lessons Learnt

Goli Haidari[1]; Naomi Fitzgerald[4]; Sonia Raffe[2]; Nneka Nwokolo[3]; Olamide Dosekun[1]; Mark D. Lawton[5]; Nickie Mackie[1]; Julie Fox[4]; Martin Fisher[2]; Sarah Fidler[1]

[1]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom; [2]Brighton and Sussex Hospitals NHS Trust, Brighton, United Kingdom; [3]Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom; [4]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [5]The Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, United Kingdom; [6]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom; [7]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [8]Brighton and Sussex Hospitals NHS Trust, Brighton, United Kingdom; [9]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom

Session S-7 Symposium — Room 613

4:00 pm – 6:00 pm

From Pathways to Paradigms: Applications of Systems Biology to HIV/Host Interactions

Target audience: This session is directed to scientists and clinicians who are interested in recent advances in the use of RNA profiling, transcriptomic analyses, microarrays, and other state-of-the-art methodologies in an integrated approach (ie, systems biology) to probe new insights and hypotheses in HIV and SIV pathogenesis, prevention, and treatment.

Level of knowledge: It is assumed that participants are familiar with the basic concepts and challenges in the fields of HIV pathogenesis, prevention, and treatment and have some familiarity with the cellular processes that underlie the molecular biology of viral-host interactions.

Objectives: At the completion of the session, participants will be able to:

- Recognize how integrative approaches to profiling RNA transcription can be applied to provide new interpretations of relevant problems in HIV pathogenesis research.
- Appreciate how a systems-biology approach can generate new hypotheses for developing novel interventions for HIV prevention and therapy.
- Discuss emerging technologies and bioinformatics analyses that have enabled molecular signatures and networks to be identified and applied to relevant questions for HIV and other infectious pathogens.

Symposium Conveners

Steven Bosinger, *Emory University, Yerkes National Primate Research Center*

Raphael Gottardo, *Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US*

171 Using Systems Approaches to Study Pathogenesis: Bridging Networks and Mechanisms

Nevan Krogan

University of California San Francisco, San Francisco, CA, US

172 Molecular Basis of T-Cell Exhaustion

E. John Wherry

University of Pennsylvania, Philadelphia, PA, US

173 A Systems Biology Approach to Identify Targets and Mechanisms of HIV Latency and HIV Eradication

Rafick P. Sekaly

Case Western Reserve University, Cleveland, OH, US

174 Translating Anti–HIV-1 Immune Mechanisms Into Clinical Interventions

Sallie R. Permar

Duke University, Durham, NC, US

Session S-8 Symposium — Room 6D

4:00 pm – 6:00 pm

Scale-Up of Interventions

Target audience: This session is directed to researchers and programmers interested in the scale-up of HIV programs around the world.

Level of knowledge: It is assumed that participants are familiar with HIV prevention methods, the impact of HIV on key populations, HIV testing approaches, laboratory assays in support of HIV prevention, and HIV care and treatment.

Objectives: At the completion of the session, participants will be able to:

- Describe scientific evidence relating to male circumcision and its programmatic scale-up for HIV prevention.
- Describe scientific bases for interventions for people who inject drugs.
- Describe recent evidence and trends concerning scale-up of HIV testing.
- Describe the role of laboratory infrastructure and systems required to support HIV/AIDS program scale-up.

Symposium Conveners

Linda-Gail Bekker, *Desmond Tutu HIV Foundation, South Africa*

Kevin M. De Cock, *Centers for Disease Control and Prevention, Nairobi, Kenya*

175 From Equipoise to Efficacy to Millions Reached With Voluntary Medical Male Circumcision for HIV Prevention

Jason B. Reed

US Department of State, Office of the Global AIDS Coordinator, Washington, DC, US

176 Scale-Up of HIV Interventions for People Who Inject Drugs: Quality and Coverage

Anna Deryabina

ICAP at Columbia University, Almaty, Kazakhstan

177 HIV Testing and Counseling: Emerging Issues, New Directions

Rachel C. Baggaley

World Health Organization, Geneva, Switzerland

178 Ten Years of Strengthening Laboratory Services and Systems: Then, Now, and the Future

John Nkengasong

US Centers for Disease Control and Prevention, Atlanta, GA, US

Session S-9 Symposium — Room 6E

4:00 pm – 6:00 pm

HCV: New Frontiers and Controversies

Target audience: This session is directed to persons who are interested in the basic science, public health impact, and management of hepatitis C virus (HCV) infections.

Level of knowledge: It is assumed that participants are familiar with general concepts of virology and medicine.

Objectives: At the completion of the session, participants will be able to:

- Describe the mechanisms by which HCV affects the liver.
- Recognize the cells that HIV infects within the liver.
- Describe the impact of HCV eradication on HCV transmission, and the pitfalls.

Symposium Conveners

Chloe M. Orkin, *Barts Health NHS Trust, London, United Kingdom*

David L. Wyles, *University of California San Diego (UCSD), La Jolla, CA, US*

179 Pathogenesis of Acute HCV Infection

Ashwin Balagopal

Johns Hopkins University School of Medicine, Baltimore, MD, US

180 HCV Treatment as Prevention: Challenges and Opportunities

Gregory Dore

University of New South Wales, Sydney, Australia

181 HCV Therapeutics: It's the Virus, Stupid

Mark S. Sulkowski

Johns Hopkins University School of Medicine, Baltimore, MD, US

182 HCV Therapeutics: Big Sticks With Big Stickers

Marion G. Peters

University of California San Francisco, San Francisco, CA, US

POSTER SESSIONS, BY CATEGORY

All poster sessions will be held in the Poster Hall from 2:30 PM to 4:00 PM on the scheduled day.

A: Virology
P-A1: Cellular Innate Immunity: Tuesday, 2/24/2015
P-A2: Nucleus Entry, Integration, and Export: Wednesday, 2/25/2015
P-A3: SAMHD1: Tuesday, 2/24/2015
P-A4: Enhancers and Inhibitors of Viral Infectivity and Entry: Thursday, 2/26/2015
P-A5: Envelopes, Receptors, and Tropism: Wednesday, 2/25/2015
P-A6: Nef Functions: Thursday, 2/26/2015

B: Molecular Epidemiology and HIV/SIV Evolution
P-B1: Viral Origins and Recombinant Forms: Thursday, 2/26/2015
P-B2: Defining Epidemiologically Linked Transmission: Tuesday, 2/24/2015
P-B3: Transmission Clusters: Wednesday, 2/25/2015
P-B4: Transmission Networks: MSM: Tuesday, 2/24/2015
P-B5: Next Generation of Next-Generation Sequencing: Thursday, 2/26/2015

C: Pathogenesis—Human Studies and Animal Models
P-C1: The Gut Microbiome: Tuesday, 2/24/2015
P-C2: The Mucosa in HIV/SIV Pathogenesis: Tuesday, 2/24/2015
P-C3: Innate and Unconventional T-Cell Responses: Wednesday, 2/25/2015
P-C4: Monocytes, Dendritic Cells, and Neutrophils: Wednesday, 2/25/2015
P-C5: Studies of HIV-Exposed Uninfected Individuals: Tuesday, 2/24/2015
P-C6: Host Factors in HIV Pathogenesis: Tuesday, 2/24/2015
P-C7: HIV/CMV Interactions in Transmission and Pathogenesis: Thursday, 2/26/2015
P-C8: Aging and Immune Senescence: Thursday, 2/26/2015
P-C9: Immune Pathogenesis of IRIS: Thursday, 2/26/2015
P-C10: Immune Activation and HIV Pathogenesis: Wednesday, 2/25/2015
P-C11: Manipulating Immune Activation: Wednesday, 2/25/2015
P-C12: Pathogenesis in Lymph Nodes: Thursday, 2/26/2015
P-C13: Dissecting Pathogenesis Through In Vitro Studies: Thursday, 2/26/2015
P-C14: Dissecting Pathogenesis Through In Vivo Studies: Thursday, 2/26/2015

E: Host Immune Responses to Infection, Vaccines, and Immunotherapy
P-E1: The Effect of HIV Infection on B Cells: Tuesday, 2/24/2015
P-E2: The Envelope/Antibody Dynamic: Tuesday, 2/24/2015
P-E3: New Approaches to Immunostimulation: Wednesday, 2/25/2015
P-E4: Cellular Immune Response to HIV: Thursday, 2/26/2015

F: HIV Persistence, Reservoirs, Latency, Eradication, including Gene Therapy
P-F1: Immune-Based Strategies in Latency: Tuesday, 2/24/2015
P-F2: Viral Reservoir Dynamics During ART: Thursday, 2/26/2015
P-F3: Cellular Factors of Latency: Thursday, 2/26/2015
P-F4: Dynamics of Latency and Reactivation: Wednesday, 2/25/2015
P-F5: Gene Editing: Wednesday, 2/25/2015
P-F6: HDAC Inhibitors: Tuesday, 2/24/2015
P-F7: Pharmacologic Latency-Reactivation Agents: Tuesday, 2/24/2015
P-F8: Latency Models and Assays: Wednesday, 2/25/2015
P-F9: Stem Cell Transplantation: Wednesday, 2/25/2015

G: Neuropathogenesis
P-G1: CNS Reservoirs: Tuesday, 2/24/2015
P-G2: Optimizing ART for HAND Treatment and Prevention: Tuesday, 2/24/2015
P-G3: Neurologic Disorders in Resource-Limited Settings: Wednesday, 2/25/2015
P-G4: HAND Genetics: Thursday, 2/26/2015
P-G5: HAND Diagnosis and Predictors: Tuesday, 2/24/2015
P-G6: Inflammation and Markers of Brain Injury in HAND: Thursday, 2/26/2015
P-G7: Aging and Cognitive Decline: Wednesday, 2/25/2015
P-G8: Mitochondrial Dysfunction in HAND and Depression: Thursday, 2/26/2015
P-G9: Neuropathogenesis Mechanisms: Thursday, 2/26/2015

H: Clinical Pharmacology
P-H1: Pharmacokinetics, Pharmacodynamics, and Adherence: Tuesday, 2/24/2015
P-H2: Pharmacogenomics: Tuesday, 2/24/2015
P-H3: Drug-Drug Interactions: Tuesday, 2/24/2015
P-H4: Pharmacokinetics in Compartments and Reservoirs and of Novel Formulations: Thursday, 2/26/2015
P-H5: New Technologies in Assessing Drug Interactions and Systemic and Intracellular Pharmacology: Thursday, 2/26/2015

I: Antiretroviral Therapy: Preclinical Studies
P-I1: Drug Development: Wednesday, 2/25/2015

J: Antiretroviral Therapy: Randomized Clinical Trials
P-J1: ART: Recent Perspectives: Tuesday, 2/24/2015

K: Antiretroviral Therapy: Observational Studies
P-K1: ART: Adherence, Adherence, Adherence: Tuesday, 2/24/2015
P-K2: ART: Monitoring and Biomarkers: Tuesday, 2/24/2015
P-K3: ART: Immunologic Response?The Good and The Bad: Wednesday, 2/25/2015
P-K4: ART: Mortality: Wednesday, 2/25/2015

L: HIV Drug Resistance
P-L1: HIV Drug Resistance: Mechanisms and Mutations: Thursday, 2/26/2015
P-L2: HIV Subtypes and Resistance: Thursday, 2/26/2015
P-L3: Transmitted HIV Drug Resistance: Assessing the Threat: Thursday, 2/26/2015
P-L4: HIV Drug Resistance: Global Perspective and Clinical Implications: Thursday, 2/26/2015

M: HIV Diagnostics
P-M1: Nucleic-Acid–Based Detection of HIV: Tuesday, 2/24/2015
P-M2: Comparison of HIV Incidence Assays: Wednesday, 2/25/2015
P-M3: HIV Detection, Tropism, and CD4 Measurement: Wednesday, 2/25/2015

N: Hepatitis Viruses
P-N1: Natural History and Prognosis of HCV Infection: Tuesday, 2/24/2015
P-N2: HCV Therapy: Observations From Cohort Studies: Tuesday, 2/24/2015
P-N3: Treatment of HCV with DAAs: Short-Term Costs and Long-Term Benefits: Tuesday, 2/24/2015
P-N4: HCV: Getting the Drugs to Those Who Need Them: Tuesday, 2/24/2015
P-N5: HCV: Epidemiology and Case Detection: Wednesday, 2/25/2015
P-N6: Acute HCV Infection: Wednesday, 2/25/2015
P-N7: Immunopathogenesis of HCV Infection: Wednesday, 2/25/2015
P-N8: HCV Therapeutics: Preclinical Observations and Clinical Trials of DAAs: Thursday, 2/26/2015
P-N9: Mental Health and Treatment Adherence with Direct-Acting Antivirals: Thursday, 2/26/2015
P-N10: HCV: Resistance to Antiviral Agents: Thursday, 2/26/2015
P-N11: Other Hepatitis Viruses: HBV, HDV, HEV: Thursday, 2/26/2015

O: HIV-Related and Non–HIV-Related Malignancies
P-O1: HPV Infections and Cancers: Tuesday, 2/24/2015
P-O2: AIDS-Related Cancers: Lymphoma and KS: Wednesday, 2/25/2015
P-O3: Cancer and Cancer Risk in HIV Subpopulations and Lung Cancer: Thursday, 2/26/2015

P: Cardiovascular Complications of HIV Infection and Antiretroviral Therapy
P-P1: Cardiovascular Disease Outcomes: Tuesday, 2/24/2015
P-P2: Dyslipidemia: Mediators and Treatment: Wednesday, 2/25/2015
P-P3: ART: Cardiovascular Risk and Hypertension: Wednesday, 2/25/2015
P-P4: What Predicts Risk for CVD in HIV? Tuesday, 2/24/2015
P-P5: Cardiovascular Risk Prediction: Wednesday, 2/25/2015
P-P6: Biomarkers and Atherosclerosis: Tuesday, 2/24/2015
P-P7: Endothelial Functions and Cerebral Vasoreactivity: Tuesday, 2/24/2015

Q: Other Complications of HIV Infection and Antiretroviral Therapy
P-Q1: Inflammation: Biomarkers and Relationship to Outcomes: Tuesday, 2/24/2015
P-Q2: Bone Metabolism and ART: Mechanisms and Outcomes: Tuesday, 2/24/2015
P-Q3: Bone Disease: Mechanisms of Bone Loss and Fracture Risk: Tuesday, 2/24/2015
P-Q4: Measuring Bone Density: Tuesday, 2/24/2015
P-Q5: Fat Without Borders: Metabolic Complications in Resource-Limited Settings: Wednesday, 2/25/2015
P-Q6: Aging: Frailty, Telomeres, and mtDNA: Tuesday, 2/24/2015
P-Q7: Diabetes and Other Endocrine Disorders: Tuesday, 2/24/2015
P-Q8: Renal Dysfunction: ART and Biomarkers: Thursday, 2/26/2015
P-Q9: Renal Transplantation: Long-Term Outcomes: Thursday, 2/26/2015
P-Q10: Pulmonary Disease: Thursday, 2/26/2015
P-Q11: Body Composition and Risk Factors for Abnormalities: Thursday, 2/26/2015
P-Q12: Complications: Liver Disease Without Viral Hepatitis: Thursday, 2/26/2015
P-Q13: Depression and Alcohol Use Disorders: Thursday, 2/26/2015

R: Tuberculosis and Other Opportunistic Infections
P-R1: Immune Reconstitution Inflammatory Syndrome in Opportunistic Infections: Tuesday, 2/24/2015
P-R2: T-Cell Responses to Tuberculosis Infection: Tuesday, 2/24/2015
P-R3: TB Diagnostic Challenges: Tuesday, 2/24/2015
P-R4: TB Adverse Events, Recurrence, and Mortality: Tuesday, 2/24/2015
P-R5: Cryptococcal Meningitis: Host Response, Treatment, and Outcomes: Thursday, 2/26/2015
P-R6: Syphilis and HIV Coinfection: Tuesday, 2/24/2015
P-R7: Opportunistic Infections: Odds and End Organs: Tuesday, 2/24/2015

S: HIV in Women and Women's Health
P-S1: Access and Engagement: Thursday, 2/26/2015
P-S2: Cervical Sampling, Shedding, and Outcomes: Tuesday, 2/24/2015
P-S3: Hormonal Contraception: Thursday, 2/26/2015

T: Maternal/Fetal HIV
P-T1: How Fast? How Often? Achieving Viral Suppression in Pregnant and Postpartum Women: Tuesday, 2/24/2015
P-T2: Rates and Risks of MTCT and HIV-Free Survival: Tuesday, 2/24/2015
P-T3: Option B+: Retention and Transmission: Tuesday, 2/24/2015
P-T4: Health Outcomes of HIV- and ARV-Exposed Infants, Children, and Youth: Thursday, 2/26/2015
P-T5: Coinfections Among HIV-Exposed Infants and Children: Thursday, 2/26/2015
P-T6: ART Adherence, Adverse Effects, and Retention Among Pregnant Women and Infants: Tuesday, 2/24/2015
P-T7: Pharmacokinetics and Safety of ART During Pregnancy: Tuesday, 2/24/2015
P-T8: Planning and Preventing Pregnancy: Tuesday, 2/24/2015
P-T9: Mechanisms of MTCT and Maternal/Infant Health: Thursday, 2/26/2015
P-T10: Immune Mechanisms in MTCT: Tuesday, 2/24/2015
P-T11: PMTCT-Associated Drug Resistance in Women and Infants: Tuesday, 2/24/2015

U: Pediatrics and Adolescents
P-U1: HIV Diagnosis in Infants and Children: Tuesday, 2/24/2015
P-U2: Early ART and HIV Persistence: Tuesday, 2/24/2015
P-U3: Treatment Outcomes Among Children and Youth With HIV: Wednesday, 2/25/2015
P-U4: Treatment and Monitoring Strategies in Children: Wednesday, 2/25/2015
P-U5: Determinants of Disease Progression in Children: Tuesday, 2/24/2015
P-U6: Complications of HIV and ART: Pulmonary and Cardiovascular Outcomes: Thursday, 2/26/2015
P-U7: Complications of HIV and ART: Bones, Brains, and Kidneys: Thursday, 2/26/2015
P-U8: Tuberculosis and Other Coinfections in Children With HIV: Wednesday, 2/25/2015
P-U9: Responses to Vaccines in Children: Tuesday, 2/24/2015
P-U10: Pharmacokinetics, Safety, and Efficacy of ART in Children and Youth: Tuesday, 2/24/2015

V: Prevention and Intervention Studies
P-V1: Postexposure Prophylaxis (PEP): Wednesday, 2/25/2015
P-V2: PrEP and Microbicide Challenge: Thursday, 2/26/2015
P-V3: PrEP: Uptake: Tuesday, 2/24/2015
P-V4: PrEP: Measures and Correlates of Adherence: Tuesday, 2/24/2015
P-V5: PrEP: Evaluating Potential Harm: Wednesday, 2/25/2015
P-V6: HIV Prevention, Miscellaneous: Thursday, 2/26/2015

W: Epidemiology
P-W1: HIV Testing and the Continuum of Care in the Industrialized World: Tuesday, 2/24/2015
P-W2: HIV Testing and the Continuum of Care in the Developing World: Tuesday, 2/24/2015
P-W3: Risk Factors for Transmission in MSM: Wednesday, 2/25/2015
P-W4: Transmission Through Needles and Heterosexual Contact: Wednesday, 2/25/2015
P-W5: Incidence and Prevalence of HIV Infection, Including Acute HIV: Thursday, 2/26/2015
P-W6: Disease Progression, Morbidity, and Mortality: Thursday, 2/26/2015
P-W7: HIV Stigma: Thursday, 2/26/2015
P-W8: Serosorting and Seroadaptive Behavior: What's Your Position? Thursday, 2/26/2015

X: Health Care Delivery and Health Systems
P-X1: Paying for Care: Tuesday, 2/24/2015
P-X2: Linkage to and Retention in Care: Wednesday, 2/25/2015
P-X3: Guidelines and Their Implementation: Thursday, 2/26/2015

Y: Implementation Science
P-Y1: Male Circumcision: Risk, Innovation, and Scale-Up: Thursday, 2/26/2015
P-Y2: Linkage to Care and ART Initiation: Wednesday, 2/25/2015
P-Y3: HIV Testing: Innovations and Scale-Up: Wednesday, 2/25/2015

Z: Population and Economic Modeling
P-Z1: Costs and Cost Effectiveness: Tuesday, 2/24/2015
P-Z2: Modeling HIV Epidemiology: Wednesday, 2/25/2015
P-Z3: Modeling the Impact of HIV Interventions: Thursday, 2/26/2015

POSTER LISTINGS, BY CATEGORY

TUESDAY, FEBRUARY 24, 2015

Session P-A1 Poster Session — Poster Hall
2:30 pm – 4:00 pm

Cellular Innate Immunity

183 STAT5 Inhibition Reduces HIV-1 Infection and TLR7/8 Responses in Human Macrophages
Sofia Appelberg[1]; Carla N. Mavian[1]; Julie C. Williams[1]; Philip Lichlyter[1]; John Sleasman[2]; Maureen M. Goodenow[2]
[1]University of Florida, Gainesville, FL, US; [2]Duke University, Durham, NC, US

184 Regulation of the Innate Immune Sensing of HIV by the Viral Capsid and the Cytosolic DNA Sensor cGAS
Nicolas Manel
Institut Curie, Paris, France

185 cGAS Induced Type I IFN Responses in Dendritic Cells From HIV Elite Controllers
Enrique Martin-Gayo[1]; Jacqueline Cronin[1]; Zhengyu Ouyang[1]; Taylor Hickman[1]; John Trombetta[2]; Florencia Pereyra[1]; Bruce Walker[1]; Alex Shalek[1]; Mathias Lichterfeld[3]; Xu Yu[1]
[1]Ragon Institute of MIT, MGH and Harvard, Boston, MA, US; [2]MIT Institute for Medical Engineering & Science, Boston, MA, US; [3]Massachusetts General Hospital, Boston, MA, US

186 Characterization of Interferon-α Subtypes in the LPAC Model
Michael Harper[1]; Kathrin Gibbert[2]; Eric Lee[1]; Kejun Guo[1]; Stephanie Dillon[1]; Martin McCarter[3]; Ulf Dittmer[2]; Cara C. Wilson[1]; Mario Santiago[1]
[1]University of Colorado Anschutz Medical Campus, Denver, CO, US; [2]University of Duisburg-Essen, Essen, Germany; [3]University of Colorado Anschutz Medical Campus, Aurora, CO, US

187 HIV Vpu Inhibits NF-kB Activity but Does Not Interfere With Interferon Regulatory Factor 3
Lara Manganaro; Elisa de Castro; Ana Maestre; Adolfo Garcia-Sastre; Ana Fernandez-Sesma; Viviana A. Simon
Icahn School of Medicine at Mount Sinai, New York, NY, US

188 HIV-1 Exploits CD169 to Evade IFNα-Induced Antiviral State in Myeloid Cells
Hisashi Akiyama[1]; Nora Ramirez[1]; Gregory Gibson[2]; Simon Watkins[2]; Zandrea Ambrose[2]; Rahm Gummuluru[1]
[1]Boston University School of Medicine, Boston, MA, US; [2]University of Pittsburgh School of Medicine, Pittsburgh, PA, US; [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, US

189 Interferon-Induced Transmembrane Proteins (IFITMs) Antagonize Postintegration Replication of HIV but Are Overcome by Viral Membrane Accessory Proteins
Wingyiu Lee; Ifrah Omar; Richard D. Sloan
Queen Mary University of London, London, United Kingdom

190 HSV-1-Induced Enhancement of HIV-1 Replication Is Dependent on Decrease in IFITM3 Levels
Viviane Andrade[1]; Milene Miranda[2]; Mario Stevenson[1]; Thiago M. Souza[2]
[1]University of Miami, Miami, FL, US; [2]Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

191 Characterization of the Activity of an Innate Immunity Protein, the Apolipoprotein L6
Nitisha Pyndiah[1]; Angela Ciuffi[1]; Amalio Telenti[2]
[1]Institute of Microbiology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [2]J Craig Venter Institute, San Diego, CA, US

192 HIV and SIV Inhibition by RNA-Associated Early Stage Antiviral Factor (REAF)
Aine McKnight
Queen Mary University of London, London, United Kingdom

193 Translational Control of APOBEC3G/F Restriction Factors by the HIV-1 Vif Protein
Camille Libre[1]; Santiago X. Guerrero[2]; Julien Batisse[1]; Roland Marquet[1]; Jean-Christophe Paillart[1]
[1]IBMC CNRS, Strasbourg, France; [2]Centre for Genomic Regulation, Barcelona, Spain

194 Evidence for Lentivirus-Driven Evolution of APOBEC3C
Cristina Wittkopp; Michael Emerman
Fred Hutchinson Cancer Research Center, Seattle, WA, US

195 Reevaluation of the Role of the Small Host Cell GTPase Rab6 in the HIV-1 Replication Cycle
Isaac Zentner; Simon Cocklin
Drexel University College of Medicine, Philadelphia, PA, US

WEDNESDAY, FEBRUARY 25, 2015

Session P-A2 Poster Session — Poster Hall
2:30 pm – 4:00 pm

Nucleus Entry, Integration, and Export

196 The Mutated Form of Transportin 3 From Patients With Limb-Girdle Muscular Dystrophy 1F Hijacks Wild-Type Transportin 3 and Interferes With CPSF6 Subcellular Localization, Impairing HIV-1 Nuclear Entry
Sara Rodriguez-Mora[1]; Mayte Coiras[1]; Mercedes Bermejo[1]; Elena Mateos[1]; Ramon Marti[2]; Juan Jesus Vilchez[3]; Antonio Luis Andreu[2]; Jose Alcami[1]
On behalf of the AIDS Immunopathogenesis Unit
[1]Instituto de Salud Carlos III, Madrid, Spain; [2]Vall d'Hebron Institut de Recerca, Barcelona, Spain; [3]Hospital Universitari i Politecnic La Fe, Valencia, Spain

197 Longitudinal Epigenome-Wide Association Study of Pre- and Post-HIV–Infected Subjects
Sophie Limou[1]; George W. Nelson[1]; Elizabeth Binns-Roemer[1]; Jia Li[1]; Fathi Elloumi[1]; James J. Goedert[3]; Cheryl A. Winkler[1]
[1]Frederick National Laboratory Operated by Leidos Biomedical Research, Inc, for the National Cancer Institute, Frederick, MD, US; [2]Frederick National Laboratory Operated by Leidos Biomedical Research, Inc, for the National Cancer Institute, Frederick, MD, US; [3]National Cancer Institute (NCI), Bethesda, MD, US

198 IN Variants Retarget HIV-1 Integration and Are Associated With Disease Progression
Frauke Christ[1]; Jonas Demeulemeester[1]; Zeger Debyser[1]; Rik Gijsbers[1]; Jan De Rijck[1]; Thumbi Ndung'u[2]; Paradise Madlala[1]
[1]KU Leuven, Leuven, Belgium; [2]University of KwaZulu-Natal, Durban, South Africa

199 HIV-1 Integration Sites in Macrophages and CD4$^+$ T Cells Are Distinct
Yik Lim Kok; Valentina Vongrad; Mohaned Shilaih; Herbert Kuster; Roger Kouyos; Huldrych F. Günthard; Karin J. Metzner
University Hospital Zurich, Zurich, Switzerland

200 A Screening for DNA Repair Enzymes That Affect HIV-1 Infection
Noriyoshi Yoshinaga[1]; Yusuke Matsui[1]; Keisuke Shindo[1]; shunichi Takeda[1]; Akifumi Takaori-Kondo[1]
[1]Kyoto University, Kyoto-shi, Japan; [2]Kyoto University, Kyoto-shi, Japan

201 The Activity of HIV-1 Rev/RRE Varies Greatly Between Isolates

Patrick E. Jackson[1]; Denis Tebit[1]; David Rekosh[1]; Marie-Louise Hammarskjold[1]

[1]University of Virginia, Charlottesville, VA, US; [2]University of Virginia, Charlottesville, VA, US

TUESDAY, FEBRUARY 24, 2015

Session P-A3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

SAMHD1

202 A Surprising New Function of SAMHD1 as a Pro-Pathogenic Factor in HIV Infection

Gilad Doitsh; Nicole Galloway; Xin Geng; Isa Monus Arias; Zhiyuan Yang; Warner C. Greene

The J. David Gladstone Institute, University of California San Francisco, San Francisco, CA, US

203 Mapping Vpx and Vpr Specificity in Antagonism of SAMHD1

Chelsea Spragg; Michael Emerman

Fred Hutchinson Cancer Research Center, Seattle, WA, US

204 Differentiation Stimuli Strongly Impact the Ability of Macrophages to Support HIV-1 Replication Due to SAMHD1 Restriction

Ester Ballana[1]; Roger Badia[1]; Eva Riveira-Muñoz[1]; Alba Ruíz[1]; Javier Torres-Torronteras[2]; Bonaventura Clotet[1]; Eduardo Pauls[1]; Ramon Marti[2]; José Esté[1]
HIV Pathogenesis Research Group

[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain; [2]Institut de Recerca Hospital Universitari Vall d'Hebron, Barcelona, Spain

205 Essential Role of Cyclin D3 in dNTP Pool Control and HIV-1 Replication in Macrophages

Ester Ballana[1]; Alba Ruíz[1]; Eduardo Pauls[1]; Javier Torres-Torronteras[2]; Roger Badia[1]; Eva Riveira-Muñoz[1]; Bonaventura Clotet[1]; Ramon Marti[2]; José Esté[1]
HIV Pathogenesis Research Group

[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain; [2]Institut de Recerca Hospital Universitari Vall d'Hebron, Badalona, Spain

206 Low SAMHD1 Expression Renders Activated and Proliferated CD4$^+$ Susceptible to HIV-1

Nabila Seddiki[1]; Nicolas Ruffin[1]; Vedran Brezar[1]; Diana Ayinde[2]; Julian Schulze zur Wiesch[3]; Jan van Lunzen[3]; Olivier Schwartz[2]; Jean-Daniel Lelièvre[1]; Jacques Banchereau[1]; Yves Lévy[1]

[1]Inserm U955 Eq16/UPEC, Créteil, France; [2]Institut Pasteur, Paris, France; [3]University Medical Center, Hamburg-Eppendorf and Heinrich-Pette-Institute, Hamburg, Germany

207 SAMHD1 Partially Blocks Lentiviral Gene Transfer Into Hematopoietic Stem Cells

Duo Li[1]; Erika Schlaepfer[1]; Annette Audigé[1]; Baek Kim[2]; Roberto Speck[1]

[1]University Hospital Zurich, Zurich, Switzerland; [2]Department of Pediatrics Emory School of Medicine, Atlanta, GA, US

THURSDAY, FEBRUARY 26, 2015

Session P-A4 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Enhancers and Inhibitors of Viral Infectivity and Entry

208 Fresh Semen Harbors HIV-Enhancing Amyloids and Decreases the Efficacy of Microbicides

Jan Munch[3]; Onofrio Zirafi[3]; Shariq Usmani[3]; Kyeong-Ae Kim[3]; Frank Kirchhoff[3]; Christopher D. Pilcher[1]; Haichuan Liu[1]; H. Ewa Witkowska[1]; Warner C. Greene[2]; **Nadia R. Roan**[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]The J. David Gladstone Institutes, San Francisco, CA, US; [3]Ulm University Medical Center, Ulm, Germany

209 Semen's HIV Enhancing Activity Is an Individual Characteristic Independent of VL

Christopher D. Pilcher; Teri Liegler; Jason Neidleman; H. Ewa Witkowska; Wendy Hartogensis; Kara Marson; Peter Bacchetti; Frederick M. Hecht; Warner C. Greene; Nadia R. Roan

University of California San Francisco, San Francisco, CA, US

210 Hyaluronan Reduces HIV Infection of CD4+ T Cells and Greatly Enhances HIV Inhibition by Tenofovir

Peilin Li; Katsuya Fujimoto; Lilly Bourguignon; Steven Yukl; Steven Deeks; Philipp Kaiser; Peggy Kim; Diane Havlir; Harry Lampiris; Joseph K. Wong

University of California San Francisco, San Francisco, CA, US

211 Alpha-defensins increase HIV transcytosis: role in STI-mediated enhanced HIV transmission

Kimyata B. Valere[1]; Aprille Rapista[1]; Alison Quayle[2]; Wuyan Lu[3]; Eliseo Eugenin[1]; Theresa Chang[1]

[1]Rutgers University-New Jersey Medical School, Willingboro, NJ, US; [2]University Health Science Center, New Orleans, LA, US; [3]University of Maryland School of Medicine, Baltimore, MD, US

212 The Design and Investigation of Mechanism of Novel Potent HIV-1 Entry Inhibitor SC12

Marina Tuyishime; Simon Cocklin

Drexel University College of Medicine, Philadelphia, PA, US

213 Optimization of vCCL2-Based CXCR4 Inhibitors by Phage Display and Rational Design

Virginie Fievez[1]; Martyna Szpakowska[1]; Karthik Arumugam[1]; Amor Mosbah[2]; Sabrina Deroo[1]; Xavier Dervillez[1]; Pierre-Arnaud Gauthier[1]; Michele Baudy-Floc'h[2]; Carole Devaux[1]; Andy Chevigné[1]

[1]CRP-sante, Laboratory of Retrovirology, 84 Rue Val Fleuri, 1526 Luxembourg, Luxembourg; [2]Université de Rennes 1, UMR CNRS 6226, Avenue du Général Leclerc, 35042 Rennes, France

214 HIV-1 Infection of Female Primary Genital Epithelial Cells After Pseudotyping With HTLV-1: Potential Driver of Sexual Transmission of HIV-1

Yuyang Tang[1]; Alvin George[1]; Oksana Petrechko[1]; Brian Imbiakha[1]; Stephanie Sweet[1]; Yuetsu Tanaka[2]; Franklin Nouvet[1]; James E. Hildreth[1]

[1]University of California Davis, Davis, CA, US; [2]University of the Ryukyus, Nishihara-cho, Japan

WEDNESDAY, FEBRUARY 25, 2015

Session P-A5 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Envelopes, Receptors, and Tropism

215 Evaluation of HIV-1 Clones for Unique Properties Associated With Transmission

Katja Klein[1]; Annette Ratcliff[2]; Gabrielle Nickel[2]; Immaculate Nankya[2]; Mike Lobritz[2]; Yong Gao[2]; Robin Shattock[3]; Eric J. Arts[1]

[1]University of Western Ontario, London, Canada; [2]Case Western Reserve University, Cleveland, OH, US; [3]Imperial College London, London, United Kingdom

216 Selection of HIV Env Mutants With Altered Trimers by EMPIRIC Saturation Mutagenesis

Maria Duenas-Decamp; Li Jiang; Dan Bolon; Paul R. Clapham

University of Massachusetts Medical School, Worcester, MA, US

217 Characterization of HIV-1 Envelopes in Acutely and Chronically Infected Injection Drug Users

Behzad Etemad[1]; Oscar A. Gonzalez[1]; Laura F. White[2]; Oliver B. Laeyendecker[3]; Greg D. Kirk[3]; Shruti Mehta[3]; **Manish Sagar**[1]

[1]Boston University School of Medicine, Boston, MA, US; [2]Boston University, Boston, MA, US; [3]Johns Hopkins University, Baltimore, MD, US

218 Phenotypic Characterization of Transmitted/Founder Virus in HIV-1 Transmission Pairs

Corinna S. Oberle[1]; Beda Joos[1]; Nottania K. Campbell[1]; David Beauparlant[1]; Herbert Kuster[1]; Corinne Schenkel[1]; Peter Rusert[1]; Alexandra Trkola[1]; Karin J. Metzner[1]; Huldrych F. Günthard[1]

[1]University Hospital Zurich, Zurich, Switzerland; [2]Institute of Medical Virology, Zurich, Switzerland

219 HIV Coreceptor Tropism Switching Is Correlated With Binding Affinity to CXCR4

Homero Vazquez[1]; Antoine Chaillon[2]; Douglas D. Richman[3]; Sara Gianella Weibel[1]; Gabriel Wagner[1]; David M. Smith[3]

[1]University of California San Diego, San Diego, CA, US; [2]Inserm UMR U966, Tours, France; [3]Veterans Affairs Medical Center, San Diego, CA, US

220 Selective Cell-Free or Cell-to-Cell HIV-1 Infection by gp41 Cytoplasmic Tail Mutants

Natasha D. Durham[1]; Benjamin K. Chen[1]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, US; [2]Icahn School of Medicine at Mount Sinai, New York, NY, US

221 Analysis of Viral Evolution in the Blood Reveals Potential Insight Into the Evolution of Macrophage Tropism

Maria M. Bednar[1]; LiHua Ping[1]; Kathryn Arrildt[1]; Christa Sturdevant[2]; Sarah B. Joseph[1]; Laura Kincer[1]; Celia LaBranche[2]; David Montefiori[2]; Myron Cohen[3]; Ronald Swanstrom[1]

[1]University of North Carolina, Durham, NC, US; [2]Duke University, Durham, NC, US; [3]University of North Carolina, Chapel Hill, NC, US

222 Mechanistic Differences in Interactions of HIV-1 and HIV-2 With Dendritic Cells

Suzanne D. Kijewski; Hisashi Akiyama; Caitlin Miller; Nora P. Ramirez; Rahm Gummuluru

Boston University School of Medicine, Boston, MA, US

223 Identification of the First Nonhuman Primate CD4 Receptor for T/F HIV-1 Isolates

Nicholas Meyerson[2]; **Amit Sharma**[1]; Gregory Wilkerson[3]; Julie M. Overbaugh[1]; Sara Sawyer[2]

[1]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [2]The University of Texas at Austin, Austin, TX, US; [3]University of Texas, MD Anderson Cancer Center, Bastrop, TX, US

224LB Vpr Increases Env Spikes on Virions to Enhance HIV-1 Replication in Nondividing Myeloid Cells

Tao Zhou[1]; Xianfeng Zhang[2]; **Yonghui Zheng**[1]

[1]Michigan State University, East Lansing, MI, US; [2]Harbin Veterinary Research Institute, Harbin, China

THURSDAY, FEBRUARY 26, 2015

Session P-A6 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Nef Functions

225 Env and Nef Cooperatively Contribute to HIV-1–Induced pDC Activation via CD4-Dependent Mechanisms

Natalia J. Reszka-Blanco[1]; Vijay Sivaraman[1]; Liguo Zhang[2]; Lishan Su[1]

[1]University of North Carolina, Chapel Hill, NC, US; [2]Key Lab of Infection and Immunity, Insitute of Biophysics, Chinese Academy of Science, Beijing, China

226 Naturally Occurring Polymorphisms in HIV-1 Nef Impair Its Functions and Decrease Viral Replication Capacity

Thomas Vollbrecht[2]; Lorelei Bornfleth[1]; Patricia Frohnen[1]; Martha J. Lewis[1]

[1]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US; [2]University of California San Diego (UCSD), La Jolla, CA, US

227 Dynamic Range of Down-Regulation of HIV-1 Entry Receptors by Primary Nef Isolates

Mako Toyoda[1]; Yoko Ogata[1]; Macdonald Mahiti[1]; Florencia Pereyra[3]; Toshiyuki Miura[2]; Bruce Walker[3]; Zabrina L. Brumme[4]; Mark A. Brockman[4]; Takamasa Ueno[1]

[1]Kumamoto University, Kumamoto, Japan; [2]University of Tokyo, Tokyo, Japan; [3]Ragon Institute of MGH, MIT and Harvard University, Cambridge, MA, US; [4]Simon Fraser University, Burnaby, Canada

228 Differential Down-Regulation of HLA Class I Allotypes by HIV-1 Nef Primary Isolates

Macdonald Mahiti[1]; Xiaofei Jia[2]; Mako Toyoda[1]; Francis Mwimanzi[1]; Bruce Walker[3]; Zabrina L. Brumme[4]; Mark Brockman[4]; Yong Xiong[2]; **Takamasa Ueno**[1]

[1]Kumamoto University, Kumamoto, Japan; [2]Yale University, New Haven, CT, US; [3]Ragon Institute of MGH, MIT and Harvard University, Boston, MA, US; [4]Simon Fraser University, Burnaby, Canada

Session P-B1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Viral Origins and Recombinant Forms

229 Geopolitical Effects in the Epidemiology of HIV-1 Subtype

Gkikas Magiorkinis[2]; Kostantinos Angelis[1]; Ioannis Mamais[1]; Angelos Hatzakis[1]; Jan Albert[3]; Glenn Lawyer[4]; Annemarie Wensing[5]; Charles Boucher[6]; Anne-Mieke Vandamme[7]; **Dimitrios Paraskevis**[1]

[1]University of Athens, Athens, Greece; [2]University of Oxford, Oxford, United Kingdom; [3]Karolinska Institutet, Stockholm, Sweden; [4]Max Planck Institute for Informatics, Saarbrücken, Germany; [5]University Medical Center Utrecht, Utrecht, Netherlands; [6]Erasmus University Medical Center, Rotterdam, Netherlands; [7]KU Leuven, Leuven, Belgium

230 The 2 Phases of HIV-1 Group O Diversification

Marie Leoz[1]; Felix Feyertag[2]; Anfumbom Kfutwah[3]; Philippe Mauclere[4]; Guillaume Lachenal[5]; Florence Damond[6]; Veronique Lemee[1]; Francois Simon[7]; David Robertson[2]; Jean-Christophe Plantier[1]

[1]University Hospital Rouen, Rouen, France; [2]Manchester University, Manchester, United Kingdom; [3]Centre Pasteur du Cameroun, Yaounde, Cameroon; [4]Direction Interarmées du Service de Santé, Noumea, New Caledonia; [5]Université Paris Diderot, Paris, France; [6]APHP CHU Bichat Claude Bernard, Paris, France; [7]APHP CHU Saint Louis, Paris, France

231 Evidence for More Major HIV-1M Lineages From the Early Stages of the HIV-1 Epidemic

Marcel Tongo Passo[1]; Wendy A. Burgers[2]; Eitel Mpoudi-Ngole[3]; Jeffrey Dorfman[1]; Darren P. Martin[4]

[1]International Center for Genetic Engineering and Biotechnology, Cape Town, Cape Town, South Africa; [2]Division of Medical Virology, University of Cape Town, Cape Town, South Africa; [3]Institute of Medical Research and Study of Medicinal Plants (IMPM), Yaoundé, Cameroon, Yaounde, Cameroon; [4]Computational Biology Group, University of Cape Town, Cape Town, South Africa

232 HIV-1/M+O Dual Infections and HIV-MO Recombinants in France From 2004 to 2014

Pierre Cappy[1]; Fabienne De Oliveira[1]; Veronique Lemee[1]; Jean-Louis Gaillard[2]; Laurence Bocquet[3]; Jean-Dominique Poveda[4]; Magali Bouvier[5]; Anne Maillard[6]; **Thomas Mourez**[1]; Jean-Christophe Plantier[1]

[1]Rouen University Hospital, Rouen, France; [2]Ambroise Paré Hospital, Paris, France; [3]Lille University Hospital, Lille, France; [4]CERBA Laboratory, Saint-Ouen L'Aumone, France; [5]Henri Mondor Hospital, Créteil, France; [6]Pontchaillou Hospital, Rennes, France

233 Evidence of Intra-Familial Transmission of an HIV-1 M/O Intergroup Recombinant Virus

Paul Alain T. Ngoupo[1]; Serge Alain Sadeuh-Mba[1]; Fabienne De Oliveira[2]; Valérie Ngono[1]; Laure Ngono[1]; Patrice Tchendjou[4]; Véronique Penlap Mbeng[3]; Richard Njouom[1]; Anfumbom Kfutwah[1]; Jean-Christophe Plantier[2]

[1]Centre Pasteur of Cameroon, Yaounde, Cameroon; [2]Virology, CHU Rouen, Rouen, France; [3]University of Yaounde I, Yaounde, Cameroon; [4]Epidemiology, Centre Pasteur of Cameroon, Yaounde, Cameroon

234 Searching for Rare HIV Strains in Rural Democratic Republic of Congo (2001–2003)

Ana S. Vallari[1]; Carole McArthur[2]; Larry Sthreshley[3]; Catherine Brennan[1]

[1]Abbott Laboratories, Chicago, IL, US; [2]University of Missouri–Kansas City, Kansas City, MO, US; [3]IMA World Health, Kinshasa, Congo (the Democratic Republic of the)

235 Clinical and Virological Characterization of CRF07_BC infection

Szu-Wei Huang[1]; Sheng-Fan Wang[1]; Chih-Hao Lee[1]; Wing-Wai Wong[2]; Hung-Chin Tsai[3]; Chia-Jui Yang[4]; Chin-Tien Wang[5]; Jaang-Jiun Wang[6]; Daniel Kuritzkes[7]; Yi-Ming A. Chen[1]

[1]Kaohsiung Medical University, Kaohsiung City, Taiwan; [2]Taipei Veterans' General Hospital, Taipei, Taiwan; [3]Kaohsiung Veterans' General Hospital, Kaohsiung City, Taiwan; [4]Far Eastern Memorial Hospital, New Taipei City, Taiwan; [5]National Yang-Ming University, Taipei, Taiwan; [6]Children's Healthcare of Atlanta and Emory University School of Medicine, Atlanta, GA, US; [7]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, US

236 Reconstructing the HIV-1 Epidemics in Burkina Faso Using Early Samples

Gonzalo Yebra[1]; Marcia L. Kalish[2]; Andrew J. Leigh Brown[1]

[1]University of Edinburgh, Edinburgh, United Kingdom; [2]Vanderbilt University, Nashville, TN, US

237 **Neutralizing Antibodies in Humans Infected With Zoonotic Simian Foamy Viruses**

Caroline Lambert[1]; Julie Gouzil[2]; Réjane Rua[1]; Edouard Betsem[3]; Antoine Gessain[1]; **Florence Buseyne**[1]

[1]Institut Pasteur, Paris, France; [2]Ecole Vétérinaire, Maison-Alfort, France; [3]University of Yaounde, Yaounde, Cameroon

TUESDAY, FEBRUARY 24, 2015

Session P-B2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Defining Epidemiologically Linked Transmission

238 **Large Phylogenetically Linked HIV Cluster in King County, Washington, 2008 to 2014**

Susan E. Buskin[1]; Joshua T. Herbeck[2]; Katelynne M. Gardner Toren[1]; Michelle R. Perry[1]; Amy Bennett[1]; Matthew R. Golden[2]

[1]Public Health—Seattle & King County, Seattle, WA, US; [2]University of Washington, Seattle, WA, US

239 **Reconciling Named Partner and Genetic Partner HIV-1 Transmission Networks in New York City**

Joel O. Wertheim[1]; Sergei L. Kosakovsky Pond[1]; Konrad Scheffler[1]; Davey M. Smith[1]; Sanjay Mehta[1]; Sharmila Shah[2]; Lisa Forgione[2]; Lucia V. Torian[2]

[1]University of California San Diego, San Diego, CA, US; [2]New York City Department of Health and Mental Hygiene, New York, NY, US

240 **Efforts to Characterize Community HIV Transmission Dynamics May Be Critically Dependent on Provision of Both Partner Services and Genetic Sequence Analysis**

Nella L. Green; Christy Anderson; Sergei L. Kosakovsky Pond; Martin Hoenigl; David M. Smith; Sanjay Mehta; Susan Little

University of California San Diego, San Diego, CA, US

WEDNESDAY, FEBRUARY 25, 2015

Session P-B3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Transmission Clusters

241 **Growth and Geographic Spread of HIV Transmission Clusters, United States, 2007-2012**

Alexandra M. Oster[1]; Joel Wertheim[2]; Ellsworth Campbell[1]; Angela L. Hernandez[1]; Neeraja Saduvala[2]; William M. Switzer[1]; M. Cheryl Ocfemia[1]; Anupama Shankar[1]; H. Irene Hall[1]

[1]US Centers for Disease Control and Prevention (CDC), Decatur, GA, US; [2]ICF International, Atlanta, GA, US

242 **HIV Transmission Networks Among the USA, Mexico, and Central America**

Santiago Avila-Rios[1]; Joel O. Wertheim[2]; Ann M. Dennis[8]; Gustavo Reyes-Terán[1]; Carlos Mejía-Villatoro[3]; Elsa Y. Palou[4]; Guillermo Porras-Cortes[6]; Juan M Pascale[5]; Marvin Manzanero[7]; Sanjay Mehta[2]

[1]National Institute of Respiratory Diseases, Mexico City, Mexico; [2]University of California San Diego (UCSD), San Diego, CA, US; [3]Roosevelt Hospital, Guatemala City, Guatemala; [4]Hospital Escuela Universitario, Tegucigalpa, Honduras; [5]Gorgas Memorial Institute for Health Studies, Panama, Panama; [6]Vivian Pellas Metropolitan Hospital, Managua, Nicaragua; [7]Ministry of Health, Belmopan, Belize; [8]University of North Carolina, Chapel Hill, NC, US

243 **Sexual Networks Across Risk Groups Persistently Contribute to Local Spread of HIV**

Marije Hofstra[1]; Tania Mudrikova[1]; Marieke Pingen[1]; Kristine Koekkoek[1]; Arjan Van Laarhoven[1]; Rob Schuurman[1]; Andy I. Hoepelman[1]; Annemarie M. Wensing[1]

[1]University Medical Center Utrecht, Utrecht, Netherlands; [2]University Medical Center Utrecht, Utrecht, Netherlands

244 **Estimation of HIV-1 Transmission During Recent Infection in Switzerland**

Alex Marzel[1]; Mohaned Shilaih[1]; Wan-Lin Yang[1]; Jürg Böni[2]; Sabine Yerly[3]; Thomas Klimkait[4]; Vincent Aubert[5]; Huldrych F. Günthard[1]; Roger Kouyos[1]
On behalf of the Swiss HIV Cohort Study (SHCS)

[1]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland; [2]Swiss National Center for Retroviruses, Zurich, Switzerland; [3]Laboratory of Virology, Geneva, Switzerland; [4]Department of Biomedicine—Petersplatz, Basel, Switzerland; [5]Division of Immunology and Allergy, Lausanne, Switzerland; [6]The Swiss HIV Cohort Study, Zurich, Switzerland

245 **Clustering of Swiss HIV Patients Not Enrolled in the Swiss HIV Cohort Study (SHCS)**

Mohaned Shilaih[1]; Alex Marzel[1]; Jörg Schüpbach[1]; Jürg Böni[1]; Sabine Yerly[2]; Thomas Klimkait[4]; Vincent Aubert[3]; Huldrych F. Günthard[1]; Roger Kouyos[1]
The Swiss HIV Cohort Study (SHCS)

[1]University Hospital Zurich, Zurich, Switzerland; [2]Geneva University Hospital, Geneva, Switzerland; [3]University Hospital Lausanne, Lausanne, Switzerland; [4]University of Basel, Basel, Switzerland; [5]University of Zurich, Zurich, Switzerland

246 **HIV Transmission Network Structure Reveals Characteristics of Bridging Individuals**

Sanjay Mehta; Joel O. Wertheim; Konrad Scheffler; Susan Little; Richard R. Garfein; Sergei L. Kosakovsky Pond; David M. Smith

University of California San Diego, La Jolla, CA, US

247 **Phylodynamic Analysis of HIV Sub-Epidemics in Mochudi, Botswana**

Vladimir Novitsky[1]; Denise Kuehnert[2]; Sikhulile Moyo[3]; Erik van Widenfeldt[3]; Lillian Okui[3]; Max Essex[1]

[1]Harvard School of Public Health, Boston, MA, US; [2]ETH Zürich, Zürich, Switzerland; [3]Botswana-Harvard AIDS Institute Partnership, Gaborone, Botswana

248 **Exploring Transmission Dynamics of HIV in Rural KwaZulu-Natal, Using Phylogenetics**

Eduan Wilkinson[1]; Siva Danaviah[1]; Justen Manasa[1]; Frank Tanser[1]; Kobus Herbst[1]; Deenan Pillay[2]; **Tulio de Oliveira**[1]
On behalf of the PANGEA_HIV Consortium

[1]University of KwaZulu-Natal, Durban, South Africa; [2]University College London, London, United Kingdom

249 **Detecting Changes in Incidence Using Phylogenetic Tools: Simulation-Based Studies Within the PANGEA_HIV Initiative**

Emma B. Hodcroft[1]; Oliver Ratmann[2]; Anne Cori[2]; Mike Pickles[2]; Samantha Lycett[3]; Manon L. Ragonnet-Cronin[1]; Matthew Hall[1]; Andrew J. Leigh Brown[1]; Christophe Fraser[2]
On behalf of the Pangea_HIV Consortium

[1]University of Edinburgh, Edinburgh, United Kingdom; [2]Imperial College London, London, United Kingdom; [3]University of Glasgow, Glasgow, United Kingdom

TUESDAY, FEBRUARY 24, 2015

Session P-B4 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Transmission Networks: MSM

250 **HIV Transmission Among Seattle Adolescents**

Joshua Herbeck[1]; Elizabeth Wolf[1]; Stephen van Rompaey[2]; Mari M. Kitahata[2]; Lisa Frenkel[1]

[1]University of Washington, Seattle, WA, US; [2]Center for AIDS Research, Seattle, WA, US

251 **Characterization of Large Cluster Viral Networks Sustaining the Montreal MSM Epidemic**

Bluma Brenner[2]; Ruxandra-Ilinca Ibanescu[2]; Daniela Moisi[2]; Isabelle Hardy[3]; Jean-Pierre Routy[1]; Joanne Otis[4]; Mark Wainberg[2]; Michel Roger[3]

[1]McGill University, Montréal, Canada; [2]Lady Davis Institute, Montreal, Canada; [3]Université de Montréal, Montreal, Canada; [4]UQAM, Montreal, Canada

252 Sources of HIV-1 Transmission in the Ongoing, Concentrated HIV Epidemic Among Men Having Sex With Men in the Netherlands Between July 1996 and December 2010

Oliver Ratmann[1]; Ard van Sighem[2]; Daniela Bezemer[2]; Alexandra Gavryushkina[3]; Peter Reiss[2]; Frank de Wolf[1]; **Christophe Fraser**[1]

[1]Imperial College London, London, United Kingdom; [2]Stichting HIV Monitoring Foundation, Amsterdam, Netherlands; [3]University of Auckland, Auckland, New Zealand

253 A Direct Comparison of Two Densely Sampled Western European HIV Epidemics: The UK and Switzerland

Manon L. Ragonnet-Cronin[1]; Mohaned Shilaih[2]; Huldrych F. Günthard[2]; Jurg Boni[2]; Sabine Yerly[3]; Valerie Delpech[4]; David Dunn[5]; Roger Kouyos[2]; Andrew J. Leigh Brown[1]
Swiss HIV Cohort Study/UK HIV Drug Resistance Database

[1]University of Edinburgh, Edinburgh, United Kingdom; [2]University Hospital Zurich, Zurich, Switzerland; [3]University Hospital Geneva, Geneva, Switzerland; [4]Public Health England, London, United Kingdom; [5]MRC CTU at UCL, London, United Kingdom

THURSDAY, FEBRUARY 26, 2015

Session P-B5 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Next Generation of Next-Generation Sequencing

254 Present Applications of a High-Throughput, Single Measure HIV Genomic Incidence Assay

Sung Yong Park[1]; Tanzy Love[2]; Nolan Goeken[1]; Robert Bolan[3]; Alan S Perelson[4]; Michael Dube[1]; **Ha Youn Lee**[1]

[1]Keck School of Medicine at University of Southern California, Los Angeles, CA, US; [2]University of Rochester School of Medicine and Dentistry, Rochester, CA, US; [3]Los Angeles Gay and Lesbian Center, Los Angeles, CA, US; [4]Los Alamos National Laboratory, Los Alamos, CA, US

255 A Comprehensive Analysis of Primer IDs to Study Heterogenous HIV-1 Populations

David Seifert[1]; Armin Töpfer[1]; Francesca Di Giallonardo[2]; Stefan Schmutz[2]; Huldrych F. Günthard[2]; Volker Roth[3]; Niko Beerenwinkel[1]; Karin J. Metzner[2]

[1]ETH Zurich, Basel, Switzerland; [2]University Hospital Zurich, Zurich, Switzerland; [3]University of Basel, Basel, Switzerland

256 Near Full Length HIV-1 Sequencing to Understand HIV Phylodynamics in Africa in Real Time

Siva Danaviah; Justen Manasa; Eduan Wilkinson; Sureshnee Pillay; Zandile Sibisi; Sthembiso Msweli; Deenan Pillay; **Tulio de Oliveira**

University of KwaZulu-Natal, Durban, South Africa

257 Pan-HIV Next-Gen Sequencing Strategy for Viral Surveillance

Michael G. Berg[1]; Julie Yamaguchi[1]; Elodie Alessandri-Gradt[2]; Jean-Christophe Plantier[2]; Catherine Brennan[1]

[1]Abbott Laboratories, Abbott Park, IL, US; [2]Virology Unit, National Reference for HIV, Rouen, France

258 PCR-Free Full Genome Characterization of Diverse HIV-1 Strains by Nextgen Sequencing

Viswanath Ragupathy[1]; Feng Gao[2]; Ana Sanchez[2]; Marco Schito[3]; Thomas Denny[2]; Michael Busch[4]; Jiangqin Zhao[1]; Christelle Mbondji[1]; SaiVikram Vemula[1]; Indira Hewlett[1]

[1]US Food and Drug Administration, Silver Spring, MD, US; [2]Duke Human Vaccine Institute and Departments of Medicine, Duke University Medical Center, Durham, NC, US; [3]Henry Jackson Foundation, DAIDS, NIAID, Bethesda, MD, US; [4]Blood Systems Research Institute/University of California San Francisco, San Francisco, CA, US

259 Full-Length Env Deep Sequencing in a Donor With Broadly Neutralizing V1/V2 Antibodies

Ben Murrell[1]; Melissa Laird[2]; Elise Landais[3]; Caroline Ignacio[1]; Ellen Paxinos[2]; Pham Phung[4]; Sergei L. Kosakovsky Pond[1]; Douglas D. Richman[1]; Pascal Poignard[3]; Davey M. Smith[1]

[1]University of California San Diego, La Jolla, CA, US; [2]Pacific Biosciences, Menlo Park, CA, US; [3]The International AIDS Vaccine Initiative Neutralizing Antibody Center, La Jolla, CA, US; [4]LabCorp, South San Francisco, CA, US

TUESDAY, FEBRUARY 24, 2015

Session P-C1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

The Gut Microbiome

260 Functional Profiling of the Gut Microbiome in HIV Infection

Yolanda Guillén; Marc Noguera-Julian; Muntsa Rocafort; Mariona Parera; Maria Casadellà; Isabel Bravo; Josep Coll; Julià Blanco; Bonaventura Clotet; Roger Paredes
MetaHIV Study Group

IrsiCaixa AIDS Res Inst, Hosp Univ Germans Trias i Pujol, Univ Autònoma de Barcelona, Badalona, Spain

261 Gut Microbiota Correlates with HIV-1 Control and Immune Status

Muntsa Rocafort; Marc Noguera-Julian; Yolanda Guillén; Mariona Parera; Maria Casadellà; Isabel Bravo; Josep Coll; Julià Blanco; Bonaventura Clotet; Roger Paredes
MetaHIV-Pheno Study Group

IrsiCaixa AIDS Res Inst, Hosp Univ Germans Trias i Pujol, Univ Autònoma de Barcelona, Badalona, Spain

262 Butyrate Reduces Pathobiont-Associated HIV-1 Infection and Activation of Gut T Cell

Jon Kibbie; Stephanie Dillon; Eric Lee; Charles Robertson; Daniel N. Frank; Martin McCarter; Cara C. Wilson

University of Colorado Anschutz Medical Campus, Aurora, CO, US

263 Maraviroc Does Not Induce Changes in the Gut Microbiome of HIV-Infected Individuals

Andrej Vitomirov; David M. Smith; Susanna R. Var; Maile Karris; Parris Jordan; Douglas D. Richman; Susan Little; Josué Pérez-Santiago

University of California San Diego, La Jolla, CA, US

264 Fecal Microbiota of HIV Controllers Is Similar to That of Non–HIV-Infected Individuals

Selma N. Alva Hernández; Sandra M. Pinto Cardoso; Norma Téllez; Akio Murakami-Ogasawara; Gustavo Reyes-Terán

National Institute of Respiratory Diseases, Research Center in Infectious Diseases, Mexico City, Mexico

265 Impact of 2 Antiretroviral Regimens on Fecal Microbial Diversity and Composition

Sandra M. Pinto Cardoso; Selma N. Alva Hernández; Norma Téllez; Akio Murakami-Ogasawara; Gustavo Reyes-Terán

National Institute of Respiratory Diseases, Mexico City, Mexico

266 Targeting Gut Dysbiosis With Prebiotics and Glutamine in HIV-Infected Subjects

Sergio Serrano-Villar[1]; Jorge Vázquez-Castellanos[2]; Alejandro Vallejo[1]; Sara Ferrando-Martínez[4]; Talía Sainz[3]; Mar Vera[5]; Santiago Moreno[1]; Andrés Moya[2]; María José Gosalbes[2]; Vicente Estrada[6]

[1]University Hospital Ramón y Cajal, Madrid, Spain; [2]FISABIO-Salud Pública, Valencia, Spain; [3]University Hospital La Paz, Madrid, Spain; [4]University Hospital Virgen del Rocío, Sevilla, Spain; [5]Centro Sandoval, Madrid, Spain; [6]University Hospital Clínico San Carlos, Madrid, Spain

Session P-C2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

The Mucosa in HIV/SIV Pathogenesis

267 Impact of Mucosal Immunity and HIV Persistence on CD4/CD8 Ratio After ART Initiation

Sergio Serrano-Villar[1]; Talía Sainz[2]; Tae Wook-Chun[3]; Netanya S. Utay[5]; Zhong-Min Ma[4]; Basile Siewe[6]; Steven Deeks[7]; Richard Pollard[4]; Christopher Miller[4]; David Asmuth[4]

[1]University Hospital Ramón y Cajal, Madrid, Spain; [2]University Hospital La Paz, Madrid, Spain; [3]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US; [4]University of California Davis, Davis, CA, US; [5]University of Texas, Galveston, TX, US; [6]Rush University Medical Center, Chicago, IL, US; [7]University of California San Francisco, San Francisco, CA, US

268 Monocyte/Macrophage Activation and Recruitment to Mucosal Sites in SIV Pathogenesis

Jan Kristoff[1]; Jenny Stock[1]; Tianyu He[1]; Bruno Andrade[2]; Benjamin Policicchio[1]; Alan Landay[3]; Ivo Francischetti[2]; Cristian Apetrei[1]; Irini Sereti[2]; **Ivona Pandrea**[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US; [3]Rush University, Chicago, IL, US

269 Rectal Tenofovir Gel Usage Is Associated With Changes in the Mucosal Proteome

Adam Burgener[1]; Laura Romas[1]; Kenzie Birse[1]; Kenneth H. Mayer[3]; Irma Febo[5]; Ross Cranston[2]; Alex Carbarballo-Dieguez[4]; Ian McGowan[2]

[1]University of Manitoba, Winipeg, Canada; [2]University of Pittsburgh, Pittsburgh, PA, US; [3]Harvard Medical School, Boston, MA, US; [4]Columbia University, New York, NY, US; [5]University of Puerto Rico, San Juan, US

270 Links Between Systemic and Mucosal Immunity in Treated HIV Infection

Talía Sainz[1]; Sergio Serrano-Villar[2]; Gregory Melcher[3]; Zhong-Min Ma[3]; Christopher Miller[3]; Netanya S. Utay[4]; Basile Siewe[5]; Paolo Troia-Cancio[3]; Elizabeth Sinclair[6]; David Asmuth[3]

[1]Hospital Universitario Gregorio Marañón, Madrid, Spain; [2]Hospital Ramon y Cajal, Madrid, Spain; [3]University of California Davis, Davis, CA, US; [4]University of Texas Medical Branch, Galveston, TX, US; [5]Rush University Medical Center, Chicago, IL, US; [6]University of California San Francisco (UCSF), San Francisco, CA, US

271 No Impact of Early Intensified Antiretroviral Therapy on Gut Immune Reconstitution

Connie J. Kim[1]; Rodney Rousseau[2]; Colin Kovacs[3]; Sanja Huibner[2]; Gabor Kandel[4]; Erika Benko[3]; Kamnoosh Shahabi[2]; Tae Wook Chun[5]; Mario Ostrowski[2]; Rupert Kaul[2]

[1]Toronto General Hospital, Toronto, Canada; [2]University of Toronto, Toronto, Canada; [3]Maple Leaf Medical Clinic, Toronto, Canada; [4]St. Michael's Hospital, Toronto, Canada; [5]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

272 Altered Properties of Mucosal NK Cell Subsets During Acute HIV-1 Infection

Alexandra Schuetz[1]; Yuwadee Phuang-Ngern[1]; Eugene Kroon[1]; Rungsun Rerknimitr[3]; Nitiya Chomchey[2]; Nittaya Phanuphak[2]; Merlin L. Robb[4]; Jerome H. Kim[4]; Mark de Souza[2]; Jintanat Ananworanich[4]

RV254/SEARCH 010 and RV304/SEARCH 013 Study Groups

[1]Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand; [2]Thai Red Cross AIDS Research Center, Bangkok, Thailand; [3]Chulalongkorn University, Bangkok, Thailand; [4]US Military HIV Research Program, Silver Spring, MD, US

273 Loss of Cervical Gamma Delta 1 T cells in HIV-Infected Women

Natasa Strbo[1]; Maria L. Alcaide[1]; Laura Romero[1]; Hector Bolivar[1]; Deborah L. Jones[1]; Eckhard R. Podack[1]; Margaret A. Fischl[1]

[1]University of Miami, Miami, FL, US; [2]University of Miami, Miami, FL, US

274 T Regulatory Cells Disrupt the CCL20-CCR6 Axis Driving Th17 Homing to the Gut

Claire Loiseau[1]; Mary Requena[1]; Michelle Cazabat[1]; Nicolas Carrere[2]; Bertrand Suc[2]; Bruno Marchou[2]; Jacques Izopet[1]; Pierre Delobel[1]

[1]Inserm, Toulouse, France; [2]Centre Hospitalier Universitaire de Toulouse, Toulouse, France

WEDNESDAY, FEBRUARY 25, 2015

Session P-C3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Innate and Unconventional T-Cell Responses

275 Effect of KIR2D-Mediated Immunity on Clinical Outcome Among CRF01_AE-Infected Thais

Masahiko Mori[1]; Nuanjun Wichukchinda[2]; Reiko Miyahara[1]; Archawin Rojanawiwat[2]; Panita Pathipvanich[3]; Toshiyuki Miura[1]; Michio Yasunami[1]; Koya Ariyoshi[1]; Pathom Sawanpanyalert[2]

[1]Institute of Tropical Medicine, Nagasaki University, Nagasaki City, Japan; [2]Ministry of Public Health, Nonthaburi, Thailand; [3]Day Care Centre, Lampang Hospital, Lampang, Thailand

276 HLA-KIR-Associated Sites in Gag and Their Effects on Clinical Outcome in Thailand

Masahiko Mori[1]; Nuanjun Wichukchinda[2]; Reiko Miyahara[1]; Archawin Rojanawiwat[2]; Panita Pathipvanich[3]; Toshiyuki Miura[1]; Michio Yasunami[1]; Koya Ariyoshi[1]; Pathom Sawanpanyalert[2]

[1]Institute of Tropical Medicine, Nagasaki University, Nagasaki City, Japan; [2]Ministry of Public Health, Nonthaburi, Thailand; [3]Day Care Centre, Lampang Hospital, Lampang, Thailand

277 In KIR3DL1/S1 Heterozygotes Are KIR3DL1 and KIR3DS1 Co-Dominantly Expressed?

Zahra Kiani[1]; Nicole F. Bernard[1]; Julie Bruneau[2]

[1]McGill University, Montreal, Canada; [2]Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Montreal, Canada

278 Disruption of Innate-Like Unconventional T-Cell Subsets in HIV-Infected Children

Alka Khaitan[1]; Adam Kravietz[1]; Ilmet Tiina[1]; Mussa Mwamzuka[2]; Fatma Marshed[2]; Cihan Tastan[1]; Aabid Ahmed[2]; Bill Borkowsky[1]; Derya Unutmaz[1]

[1]New York University School of Medicine, New York, NY, US; [2]Bomu Hospital, Mombasa, Kenya; [3]New York University School of Medicine, New York, NY, US

279 HIV-1 Alters Innate Immune Response to BCG, Which Differs From SIV Infected Mangabeys

Melanie Gasper; David Sherman; **Donald Sodora**

Seattle Biomed, Seattle, WA, US

280 High-Level Replication Allows SHIVs to Overcome the Macaque Interferon Response

David F. Boyd; Amit Sharma; Julie M. Overbaugh

Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US

281 Elevated IFN-γ in HIV Patients Using a Novel Assay for Adaptive and Innate Immunity

Michelle K. Yong[1]; Paul Cameron[1]; Tim Spelman[2]; Julian Elliott[1]; Christopher Fairley[4]; Jeffrey Boyle[3]; Misato Miyamasu[3]; Sharon R. Lewin[1]

[1]Monash University/Alfred Hospital, Melbourne, Australia; [2]Burnet Institute, Melbourne, Australia; [3]Qiagen, Melbourne, Australia; [4]Melbourne Sexual Health Centre, Melbourne, Australia

282 TLR8 Regulation of LILRA3 Is Abrogated in HIV Infection and Correlates to CD4 Counts and Virus Loads

Hui Zhi Low; Gerrit Ahrenstorf; Torsten Witte

Hannover Medical School, Hannover, Germany

Session P-C4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Monocytes, Dendritic Cells, and Neutrophils

283 Siglec-1 on Monocytes From Untreated HIV-1–Infected Patients Enhances HIV-1 Transfer

Maria Pino; Susana Benet; Itziar Erkizia; Judith Dalmau; Dan Ouchi; Bonaventura Clotet; Javier Martínez-Picado; Nuria Izquierdo-Useros

IrsiCaixa Institute for AIDS Research, Badalona, Spain

284 Soluble CD40 Ligand Contributes to Dendritic Cell Mediated T-Cell Dysfunction

Elizabeth A. Miller; Ramya Gopal; Vanessa Valdes; Jeffrey S. Berger; Nina Bhardwaj; **Meagan O'Brien**

Icahn School of Medicine at Mount Sinai, New York, NY, US

285 The Alarmin HMGB1 Is Crucial for the Acquisition of Antiviral pDC Effector Functions

Hela Saïdi[1]; Marlène Bras[1]; Pauline Formaglio[1]; Bruno Charbit[1]; Marie-Thérèse Melki[2]; Marie-Lise Gougeon[1]

On behalf of the Antiviral Immunity, Biotherapy and Vaccine Unit

[1]Institut Pasteur, Paris, France; [2]Sebia, Evry, France

286 Dysfunctional Neutrophil Responses to SIV Infection

Tiffany Hensley-McBain[1]; Laura E. Richert-Spuhler[1]; Jillian Gile[1]; Melon T. Nega[2]; Thomas H. Vanderford[2]; Jacob D. Estes[3]; Brandon F. Keele[3]; Nichole R. Klatt[1]

[1]University of Washington, Seattle, WA, US; [2]Emory University, Atlanta, GA, US; [3]Frederick National Laboratory for Cancer Research, Frederick, MD, US

TUESDAY, FEBRUARY 24, 2015

Session P-C5 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Studies of HIV-Exposed Uninfected Individuals

287 HIV-Exposed Seronegative MSM Have Increased Novel Antiviral Factors in Rectal Mucosa

Laura Romas[1]; Klara Hasselrot[2]; Kristina Broliden[2]; Carolina Herrera[3]; Garrett Westmacott[4]; Francis Plummer[4]; Terry B. Ball[4]; Adam Burgener[1]

[1]University of Manitoba, Winnipeg, Canada; [2]Karolinska Institutet, Stockholm, Sweden; [3]Imperial College London, London, United Kingdom; [4]Public Health Agency of Canada, Winnipeg, Canada

288 PBMC From Highly Exposed Seronegative Individuals Inhibit Transmitted Founder HIV

Kevin C. Olivieri[1]; Eunyoung Kim[3]; Susan Little[5]; Michael Turchin[4]; Vanessa Serrano[1]; Amna Rasheed[2]; Quy Nguyen[1]; Paul Dejesus[1]; Steven Wolinsky[3]; Sumit Chanda[1]

[1]Sanford-Burnham Medical Research Institute, San Diego, CA, US; [2]University of California Los Angeles (UCLA), Los Angeles, CA, US; [3]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [4]University of Chicago, Chicago, IL, US; [5]University of California San Diego (UCSD), San Diego, CA, US

289 HIV-1-Exposed Seronegative Persons Have Lower Mucosal Innate Immune Reactivity

Jennifer A. Fulcher[1]; Jennifer C. Hoffman[1]; Laura M. Romas[2]; Karen Tanner[1]; Terry Saunders[1]; Julie Elliott[1]; Adam D. Burgener[2]; Peter A. Anton[1]; Otto O. Yang[1]

[1]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US; [2]University of Manitoba, Winnipeg, Canada

290 Increased Levels of Regulatory T-cells Correlate With Protection From HIV Infection

Laura Pattacini[1]; Jared Baeten[2]; Katherine Thomas[2]; **Tayler Fluharty**[1]; Pamela Murnane[2]; Deborah Donnell[2]; Nelly Mugo[2]; Jairam R. Lingappa[2]; Connie Celum[2]; Jennifer Lund[1]

[1]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [2]University of Washington, Seattle, WA, US

Session P-C6 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Host Factors in HIV Pathogenesis

291 Estimating the Respective Contributions of Human and Viral Genetic Variation to HIV Control

István Bartha[1]; Paul J. McLaren[1]; Chanson J. Brumme[2]; Richard Harrigan[2]; Amalio Telenti[3]; Jacques Fellay[1]

[1]École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; [2]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; [3]J. Craig Venter Institute, La Jolla, CA, US

292 Host Gene Expression Profiles and HIV-1 Infection Outcomes

Romel D. Mackelprang[1]; Ali Filali[2]; Mark Cameron[2]; Rafick P. Sekaly[2]; Elly Katabira[3]; Allan Ronald[4]; Glenda Gray[5]; Connie Celum[1]; M Juliana McElrath[5]; Jairam R. Lingappa[1]

[1]University of Washington, Seattle, WA, US; [2]Case Western Reserve University, Cleveland, OH, US; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]University of Manitoba, Winnipeg, Canada; [5]Fred Hutchinson Cancer Research Center, Seattle, WA, US

293 Refinement of Association Signals Assessment of Residual Heritability in Host Control of HIV Viral Load

Paul J. McLaren; **Istvan Bartha**; Jacques Fellay

École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

294 Genetic and Clinical Predictors of CD4 Recovery During Suppressive cART: WIHS

Ruth M. Greenblatt[1]; Kord Kober[1]; Peter Bacchetti[1]; Ross Boylan[1]; Kathryn Anastos[2]; Mardge Cohen[5]; Mary A. Young[3]; Deborah Gustafson[4]; Bradley Aouizerat[1]
On behalf of the WIHS

[1]University of California San Francisco, San Francisco, CA, US; [2]Montefiore Medical Center, University Hospital for Albert Einstein College of Medicine, New York, NY, US; [3]Georgetown University, Washington, DC, US; [4]State University of New York, Downstate, Brooklyn, NY, US; [5]CORE Center, Chicago, IL, US; [6]National Institutes of Health (NIH), Bethesda, MD, US

295 Host Genetic Predictors of Plasma Kynurenine/Tryptophan Among Treated HIV+ Ugandans

Sulggi A. Lee[1]; Joel Mefford[1]; Yong Huang[1]; John S. Witte[1]; Jeffrey Martin[1]; David R. Bangsberg[2]; Taisei Mushiroda[3]; Michiaki Kubo[3]; Deanna Kroetz[1]; Peter W. Hunt[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Massachusetts General Hospital and Harvard University, Boston, MA, US; [3]RIKEN Center for Genomic Medicine, Wako, Japan

296 Regulation of IL-32 Expression by a Promoter Polymorphism and MicroRNA29b in HIV-1 Patients

Carolina Scagnolari; Giulia Cacciotti; Carla Selvaggi; Noemi Giustini; Ivano Mezzaroma; Massimo Gentile; Gabriella D'Ettorre; Ombretta Turrziani; Vincenzo Vullo; Guido Antonelli

Sapienza University of Rome, Rome, Italy

297 LILRA3 Deletion Is a Genetic Risk Factor of HIV Infection

Gerrit Ahrenstorf[1]; Hui Zhi Low[1]; Katja kniesch[1]; Matthias Stoll[1]; Dirk Meyer-Olson[1]; Torsten Matthias[2]; Reinhold E. Schmidt[1]; Torsten Witte[1]

[1]Hannover Medical School, Hannover, Germany; [2]AESKU Diagnostics, Wendelsheim, Germany

298LB SIV Infection Triggers Endothelial Dysfunction and Diminished Expression of Krüppel-Like Factor 2 (KLF2) in Nonhuman Primates

Soumya Panigrahi[1]; Michael L. Freeman[1]; joseph C. mudd[4]; Nicholas Funderburg[2]; Scott Sieg[1]; David A. Zidar[1]; Mirko Paiardini[3]; Francois Villinger[3]; Mukesh K. Jain[1]; michael lederman[1]

[1]Case Western Reserve University/University Hospitals Medical Center, Cleveland, OH, US; [2]Ohio State University School of Health and Rehabilitation Sciences, Columbus, OH, US; [3]Emory University, Atlanta, GA, US; [4]Lab of Molecular Microbiology, Bethesda, MD, US

299LB A Novel Method Using ^2H_2O to Measure Collagen Turnover in HIV-Infected Individuals

Leslie R. Cockerham[1]; Claire Emson[2]; Ma Somsouk[1]; Kara Harvill[1]; Kevin Li[2]; Scott M. Turner[2]; Martin L. Decaris[2]; Marc K. Hellerstein[3]; Steven G. Deeks[1]; Hiroyu Hatano[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]KineMed, Inc, Emeryville, CA, US; [3]University of California Berkeley, Berkeley, CA, US

THURSDAY, FEBRUARY 26, 2015

Session P-C7 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HIV/CMV Interactions in Transmission and Pathogenesis

300 Effect of CMV and HIV Replication on T-Cell Exhaustion and Senescence During ART

Jennifer M. Dan[1]; Marta Massanella[1]; David M. Smith[1]; Eric S. Daar[2]; Michael P. Dube[3]; Richard Haubrich[1]; Sheldon Morris[1]; Sara Gianella Weibel[1]

[1]University of California San Diego, La Jolla, CA, US; [2]Harbor–University of California Los Angeles Medical Center, Torrance, CA, US; [3]University of Southern California Keck School of Medicine, Los Angeles, CA, US

301 HIV Myeloid Derived Suppressor Cells Control Cytomegalovirus Inflammation by IL-27

Ankita Garg; Stephen Spector

University of California San Diego, La Jolla, CA, US

302 Persistent Elevation of Inflammation Markers in HIV+ Persons With CMV Disease

Melissa Schechter[1]; Bruno Andrade[2]; Eleanor M. Wilson[1]; Virginia Sheikh[2]; Sonya Krishnan[2]; Margaret Caplan[1]; Gregg Roby[2]; Adam Rupert[3]; Peter Burbelo[4]; Irini Sereti[2]

[1]NIAID, Leidos Biomedical Inc., Fredrick, MD, US; [2]National Institute of Allergy and Infectious Diseases, Bethesda, MD, US; [3]NIAID, Leidos Biomedical Inc., Fredrick, MD, US; [4]National Institute of Dental and Craniofacial Research, Bethesda, MD, US

303 sCD163 Increase in HIV/CMV-Coinfected Subjects Included in ICONA Cohort

Serena Vita[3]; Miriam Lichtner[1]; Giulia Marchetti[2]; Claudia Mascia[3]; Esther Merlini[2]; Paola Cicconi[2]; Vincenzo Vullo[3]; Pier Luigi Viale[5]; Alberto Costantini[4]; Antonella d'Arminio Monforte[2]
For the Icona Foundation Study

[1]University of Rome La Sapienza, Polo Pontino, Latina, Italy; [2]San Paolo Hospital, Milano, Italy; [3]University of Rome La Sapienza, Rome, Italy; [4]University of Ancona, Ancona, Italy; [5]University of Bologna, Bologna, Italy

304 Genital CMV Shedding Predicts Syphilis Acquisition in HIV-Infected MSM on ART

Sara Gianella Weibel[1]; David M. Smith[1]; Eric Daar[2]; Michael Dube[3]; Andrea Lisco[4]; Christophe Vanpouille[5]; Richard Haubrich[1]; Sheldon Morris[1]

[1]University of California San Diego, La Jolla, CA, US; [2]Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, US; [3]University of Southern California Keck School of Medicine, Los Angeles, CA, US; [4]National Institute of Allergy and Infectious Diseases, Bethesda, MD, US; [5]National Institute of Child Health and Human Development, Bethesda, MD, US

Session P-C8 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Aging and Immune Senescence

305 Early Start of ART Affects Late Markers of Immune Senescence

Sharon L. Karmon; Teresa H. Evering; Melissa La Mar; Martin Markowitz

Aaron Diamond AIDS Research Center, an Affiliate of the Rockefeller University, New York, NY, US

306 Chronic HIV Infection Exacerbates Cellular Aging Markers in Isolated T-Cell Subsets

Anthony Hsieh; Beheroze Sattha; Hélène Côté
CIHR Team in Cellular Aging and HIV Comorbidities in Women and Children (CARMA cohort)

University of British Columbia, Vancouver, Canada

307 Age Associated Increases in Markers of Microbial Translocation and Inflammation in HIV-1 Infection

Eileen Scully[1]; Ainsley Lockhart[1]; Lisa Huang[2]; Marisol Romero-Tejeda[1]; Mary Albrecht[4]; Chrstine D. Palmer[1]; Ronald Bosch[3]; Marcus Altfeld[1]; Daniel Kuritzkes[2]; Nina Lin[5]

[1]Ragon Institute of MGH, MIT and Harvard, Jamaica Plain, MA, US; [2]Brigham and Women's Hospital, Boston, MA, Boston, MA, US; [3]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [4]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US; [5]Boston University School of Medicine, Boston, MA, US

Session P-C9 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Immune Pathogenesis of IRIS

308 Vitamin D, D-Dimer, IFNy and sCD14 Predict IRIS in a Prospective Multicenter Study

Laura W. Musselwhite[1]; Ann Tierney[2]; Susan Ellenberg[2]; Pablo F. Belaunzarán-Zamudio[5]; Adam Rupert[3]; Ian Sanne[4]; Michael M Lederman[6]; Juan Sierra-Madero[5]; Irini Sereti[7]

[1]Duke University, Durham, NC, US; [2]University of Pennsylvania, Philadelphia, PA, US; [3]Leidos Biomedical Inc., Reston, VA, US; [4]University of the Witwatersrand, Johannesburg, South Africa; [5]Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico; [6]Case Western Reserve University, Cleveland, OH, US; [7]National Institutes of Health (NIH), Bethesda, MD, US

309 LC-MS Analysis of Metabolites Differentiating IRIS From Non-IRIS in ACTG Study A5221

Mary A. De Groote[1]; Laura Ashton[1]; Marisa Harton[1]; Sam Bokatzien[2]; Kristofor Webb[1]; Carlos Adriano Matos de Silva[1]; Reem Al-Mubarak[1]; Sebabratra Mahapatra[1]; Diane Havlir[3]; John Belisle[1]

[1]Colorado State University, Fort Collins, CO, US; [2]National Jewish Health, Denver, CO, US; [3]University of California San Francisco, San Francisco, CA, US

310 Associations Between Plasma Cytokine and Microbial Translocation Biomarkers and IRIS

Margaret A. Fischl[2]; Linda J. Harrison[1]; Varghese George[2]; Margaret Roach[2]; Xiao-Dong Li[3]; David Asmuth[3]; Pablo Tebas[4]; Camlin Tierney[1]; Catherine Godfrey[5]; Savita Pahwa[2]

[1]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, US; [2]University of Miami Miller School of Medicine, Miami, FL, US; [3]University of California Davis, Sacramento, CA, US; [4]University of Pennsylvania, Philadelphia, PA, US; [5]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

311 Potential Role of IL-1 and IL-10 Pathways in IRIS Pathogenesis

Ainhoa Perez-Diez; **Elizabeth Richards**; Stig Jensen; Eleanor M. Wilson; Virginia Sheikh; Maura M. Manion; Bruno Andrade; Timothy Myers; Irini Sereti

National Institute of Allergy and Infectious Diseases (NIAID), Rockville, MD, US

WEDNESDAY, FEBRUARY 25, 2015

Session P-C10 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Immune Activation and HIV Pathogenesis

312 Inflammatory Biomarkers Decline but Do Not Normalize After 10 Years of cART

Kenneth A. Lichtenstein[1]; Carl Armon[2]; Vijaya Knight[1]; Rafeul Alam[1]

[1]National Jewish Health, Denver, CO, US; [2]Children's Hospital Colorado, Aurora, CO, US

313 Persistently High IL-18 and sCD14 Are Independently Associated With Clinical Failure

Ashwin Balagopal[1]; Nikhil Gupte[1]; James Hakim[2]; Mina C. Hosseinipour[3]; Nagalingeswaran Kumarasamy[4]; Andrea Cox[1]; Ian Sanne[7]; David Asmuth[5]; Thomas Campbell[6]; Amita Gupta[1]
On behalf of the ACTG

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe; [3]University of North Carolina, Chapel Hill, NC, US; [4]Y.R.G. Care, Chennai, India; [5]University of California San Diego, San Diego, CA, US; [6]University of Colorado, Denver, CO, US; [7]ACTG, Washington, DC, US

314 Impact of Partner HIV Status on Immune Activation and Inflammation During Chronic HIV

Shameem Z. Jaumdally[1]; Pamela Gumbi[1]; Hoyam Gamieldien[1]; Anabela Picton[2]; Caroline Tiemessen[2]; Lindi Masson[1]; Lenine Liebenberg[3]; David Coetzee[1]; Anna-Lise Williamson[1]; Jo-Ann Passmore[1]

[1]University of Cape Town, Cape Town, South Africa; [2]National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg, South Africa; [3]Centre for AIDS Programme Research in South Africa, Durban, South Africa; [4]University of Cape Town, Cape Town, South Africa

315 Pretherapy Inflammation and Long-Term CD4 Response to Antiretroviral Therapy

Amit C. Achhra[1]; Andrew N. Phillips[2]; Sean Emery[1]; Rodger D. MacArthur[3]; Hansjakob Furrer[4]; Stéphane De Wit[5]; Marcelo H. Losso[6]; Matthew G. Law[1]
On behalf of the INSIGHT SMART and FIRST Study groups

[1]Kirby Institute, University of New South Wales, Sydney, Australia; [2]University College London, London, United Kingdom; [3]Wayne State University, Detroit, MI, US; [4]University Hospital Bern, Bern, Switzerland; [5]Saint-Pierre University Hospital, Brussels, Belgium; [6]Hospital J.M. Ramos Mejía, Buenos Aires, Argentina

316 Plasma Levels of sCD163 Predict All-Cause Mortality From HIV Infection

Troels Bygum Knudsen[1]; Janne Petersen[2]; Holger Jon Møller[3]; Søren Moestrup[4]; Jesper Eugen-Olsen[2]; Gitte Kronborg[1]; Thomas Benfield[1]

[1]Copenhagen University Hospitals, Hvidovre, Copenhagen, Denmark; [2]Copenhagen University Hospitals, Hvidovre, Copenhagen, Denmark; [3]Aarhus University Hospital, Aarhus, Denmark; [4]Aarhus University, Aarhus, Denmark

317 Immunologic Pathways That Predict Mortality in HIV+ Ugandans Initiating ART

Sulggi A. Lee[1]; Helen Byakwaga[2]; Yap Boum[2]; Tricia Burdo[3]; Yong Huang[1]; Jessica Haberer[5]; Annet Kembabazi[2]; David R. Bangsberg[5]; Jeffrey Martin[1]; Peter W. Hunt[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Mbarara University of Science and Technology, Mbarara, Uganda; [3]Boston College, Boston, MA, US; [4]University of California San Francisco, San Francisco, CA, US; [5]Massachusetts General Hospital and Harvard University, Boston, MA, US

318 Immune Activation Impairs Yellow Fever Vaccine Efficacy in HIV-Infected Patients

Vivian I. Avelino-Silva[1]; Karina T. Miyaji[1]; Marisol Simoes[2]; Marcos Freire[2]; Ana Sartori[1]; Peter W. Hunt[3]; Karine Milani[1]; Augusto Mathias[1]; Ana Paula Batista[1]; Esper G. Kallas[1]

[1]University of Sao Paulo Medical School, Sao Paulo, Brazil; [2]Fundaçao Oswaldo Cruz, Rio de Janeiro, Brazil; [3]University of California San Francisco, San Francisco, CA, US; [4]University of Sao Paulo Medical School, Sao Paulo, Brazil

319 Association Between sCD163 and CMV IgG in Virologically Suppressed HIV+ Patients

Aimee Hodowanec[1]; Brett Williams[1]; Barbara Hanson[1]; Britt Livak[2]; Sheila Keating[3]; Nell Lurain[1]; Oluwatoyin M. Adeyemi[4]

[1]Rush University Medical Center, Chicago, IL, US; [2]University of Chicago, Chicago, IL, US; [3]Blood Systems Research Institute/University of California San Francisco, San Francisco, CA, US; [4]Ruth M Rothstein CORE Center, Chicago, IL, US

Session P-C11 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Manipulating Immune Activation

320 The mTORC1 Inhibitors, Temsirolimus and Everolimus, Suppress HIV Patient-Derived CD4+ T-Cell Death and Activation In Vitro

Clovis S. Palmer[1]; Matias Ostrowski[4]; Jingling Zhou[1]; Linda Lam[1]; Alan Landay[2]; Anthony Jaworowski[1]; Joseph M. McCune[3]; Suzanne M. Crowe[1]

[1]Burnet Institute, Melbourne, Australia; [2]Rush University Medical Center, Chicago, IL, US; [3]University of California San Francisco, San Francisco, CA, US; [4]Instituto de Investigaciones Biomédicas en Retrovirus y SIDA, Buenos Aires, Argentina

321 Decreased Monocyte Activation With Daily Acyclovir Use in HIV-1/HSV-2 Coinfected Women

Andrew D. Redd[1]; Kevin Newell[2]; Eshan U. Patel[1]; Fred Nalugoda[3]; Paschal Ssebbowa[3]; Sarah Kaliballa[3]; Ronald H. Gray[4]; Thomas C. Quinn[1]; David Serwadda[5]; **Steven J. Reynolds**[1]

[1]National Institute of Allergy and Infectious Diseases (NIAID), Washington, DC, US; [2]Clinical Research Directorate/Clinical Monitoring Research Program, Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, MD, US; [3]Rakai Health Sciences Program, Kalisizo, Uganda; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]Makerere University College of Health Sciences, Kampala, Uganda

322 Atorvastatin Reduced T-Cell Activation and Exhaustion Among Suboptimal Immune Responders: A Randomized Crossover Placebo Controlled Trial

Damalie Nakanjako

Makerere University Infectious Diseases Institute, Kampala, Uganda

323 P2X Type Purinergic Antagonists Can Block HIV-1 Infection and Associated Inflammation

Talia Swartz; Meagan O'Brien; Anthony Esposito; Nina Bhardwaj; Benjamin Chen

Icahn School of Medicine at Mount Sinai, New York, NY, US

THURSDAY, FEBRUARY 26, 2015

Session P-C12 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Pathogenesis in Lymph Nodes

324 $CD4^+$ T cell death mediated by pyroptosis in early SIV infected lymphatic tissues

Wuxun Lu[1]; Guobin Kang[1]; Fangrui Ma[1]; Yanmin Wan[2]; Yue Li[1]; Mark Lewis[3]; Qingsheng Li[1]

[1]University of Nebraska-Lincoln, Lincoln, NE, US; [2]Shanghai Public Health Clinical Center and Institutes of Biomedical Sciences, Fudan University, Shanghai, China; [3]BIOQUAL, Inc., Rockville, MD, US

325 Fibrosis in Lymphoid Tissue Is Associated With Peripheral Blood Regulatory T Cells

Julie C. Gaardbo[1]; Patricia S. Nielsen[2]; Lise Mette R. Gjerdrum[3]; Karoline Springborg[4]; Elisabeth Ralfkiær[4]; Henrik Ullum[4]; Åse Andersen[4]; **Susanne D. Poulsen**[4]
Dr. Susanne D Poulsen, sdn@dadlnet.dk

[1]University of Copenhagen, Rigshospitalet, Copenhagen, Denmark; [2]Aarhus University Hospital, Denmark, Aarhus, Denmark; [3]Bispebjerg Hospital, University Hospital of Copenhagen, Denmark, Copenhagen, Denmark; [4]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

326 Decreased T_{FR}/T_{FH} Ratio in SIV-Infected Rhesus Macaques

Ankita Chowdhury; Perla Del Río-Estrada; Steven Bosinger; Guido Silvestri

Emory University, Atlanta, GA, US

Session P-C13 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Dissecting Pathogenesis Through In Vitro Studies

327 A Dual-Tropic HIV-1 Env Interacts With CCR5 to Deplete Bystander CD4 T Cells In Vitro and In Vivo

Li-Chung Tsao[1]; Haitao Guo[2]; Jerry Jeffrey[3]; James A. Hoxie[4]; Lishan Su[2]

[1]University of North Carolina, Carrboro, NC, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]GSK, Chapel Hill, NC, US; [4]University of Pennsylvania, Philadelphia, PA, US

328 Investigation of the Association of Gag-Protease Dependent Replication Capacities With Clinical Outcomes of HIV-1 Infection

Keiko Sakai[1]; Takayuki Chikata[1]; Hiroyuki Gatanaga[2]; Shinichi Oka[2]; Masafumi Takiguchi[1]

[1]Kumamoto University, Kumamoto-shi, Japan; [2]National Center for Global Health and Medicine, Tokyo, Japan

329 Association of Bacteria-Induced IL-23 and Th17 Frequencies in HIV-1^+ Individuals

Jennifer Manuzak[1]; Sonia Amraoui[1]; Nipa Decroix[2]; Pierre Loulergue[2]; Odile Launay[2]; Marco Iannetta[1]; Jean-Baptiste Guillerme[1]; Lene Vimeux[1]; Anne Hosmalin[1]

[1]Inserm U1016, Institut Cochin, Paris, France; [2]Centre d'Investigation Clinique CIC 1417, Inserm-AP-HP, Hôpital Cochin, Paris, France

330 Effect of Methamphetamine Use on T-Cell Proliferation In Vivo and Ex Vivo

Marta Massanella[4]; Sara Gianella[4]; Jennifer M. Dan[1]; Eric Daar[2]; Michael P. Dube[3]; Richard H. Haubrich[4]; Douglas D. Richman[4]; Davey M. Smith[4]; Sheldon Morris[4]; Rachel D. Schrier[4]

[1]La Jolla Institute of Allergy and Immunology, La Jolla, CA, US; [2]Los Angeles Biomedical Research Institute at Harbor–University of California Los Angeles Medical Center, Torrance, CA, US; [3]University of Southern California Keck School of Medicine, Los Angeles, CA, US; [4]University of California San Diego, La Jolla, CA, US

Session P-C14 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Dissecting Pathogenesis Through In Vivo Studies

331 A Random Forest Approach to Define Immunological Thresholds for CD4 Recovery in HIV-Treated Individuals

Josué Pérez-Santiago[1]; **Marta Massanella**[1]; Dan Ouchi[2]; Elisabet Gómez[2]; Cecilia Cabrera[2]; Bonaventura Clotet[3]; Eugenia Negredo[3]; Julià Blanco[2]

[1]University of California San Diego, La Jolla, CA, US; [2]IrsiCaixa Institute for AIDS Research, Badalona, Spain; [3]Lluita Contra la Sida Foundation, Germans Trias i Pujol University Hospital, Badalona, Spain

332 Disease Progression in HIV Controllers; Uptake and Outcome of Antiretroviral Therapy

Jane R. Deayton[1]; Katherine C. Groves[2]; David F. Bibby[2]; Duncan A. Clark[2]; Iain Reeves[3]; Jane Anderson[3]; Chloe M. Orkin[4]; Eithne O'Sullivan[1]; Áine McKnight[1]

[1]Barts and the London, Que, London, United Kingdom; [2]Barts Health NHS Trust, London, United Kingdom; [3]Homerton University Hospital NHS Foundation Trust, London, United Kingdom; [4]Barts Health NHS Trust, London, United Kingdom

333 Immunological and Virological Progression in HIV Controllers

Nicolas Noel[1]; Nathalie Lerolle[1]; Camille Lecuroux[2]; Cécile Goujard[1]; Alain Venet[2]; Asier Sáez-Cirión[3]; Véronique Avettand-Fenoel[4]; Laurence Meyer[5]; Faroudy Boufassa[5]; Olivier Lambotte[1]
ANRS CO21/CODEX Study Group

[1]APHP, Service de Médecine Interne et Immunologie Clinique, Hôpital Bicêtre, Le Kremlin-Bicêtre, France, Le Kremlin Bicêtre, France; [2]Inserm U1012, Régulation de la Réponse Immune, Infection VIH1 et Autoimmunité, Le Kremlin Bicêtre, France; [3]Institut Pasteur, Unité de Régulation des Infections Rétrovirales, Paris, France; [4]APHP, Service de Virologie, Hôpital Necker – Enfants Malades, Paris, France; [5]Inserm U1018, Centre de Recherche en Epidémiologie et Santé des Populations, Université Paris Sud, Le Kremlin-Bicêtre, France

334 HIV Replication History Is Associated With Plasma IL-7 Levels in Aviremic Youths

Daniel Scott-Algara[1]; Jerome Lechenadec[2]; Josiane Warszawski[2]; Thomas Montange[1]; Jean-Paul Viard[3]; Catherine Dollfus[3]; Véronique Avettand-Fenoel[4]; Christine Rouzioux[4]; Stéphane Blanche[3]; **Florence Buseyne**[1]

[1]Institut Pasteur, Paris, France; [2]Inserm, Le Kremlin-Bicêtre, France; [3]AP-HP, Paris, France; [4]Université Paris Descartes, Paris, France

335 Enhanced Immune Reconstitution With Initiation of ART at HIV-1 Seroconversion (PHI)

Sabine I. Kinloch[1]; Colette Smith[1]; Kwong Tsz-Shan[2]; Jayne Ellis[2]; Margaret Johnson[2]

[1]University College London, London, United Kingdom; [2]Royal Free London NHS Foundation Trust, London, United Kingdom

336 cART-Driven Recovery of Immune Function Preferentially Targeting CXCR4-Tropic HIV-1

Joëlle Bader[1]; Martin Däumer[2]; Jürg Böni[4]; Meri Gorgievski[3]; Thomas Klimkait[1]
The Swiss HIV Cohort Study

[1]University of Basel, Basel, Switzerland; [2]Institute for Immunogenetics, Kaiserslautern, Germany; [3]University of Berne, Berne, Switzerland; [4]Swiss National Center for Retroviruses, Zürich, Switzerland

337 Repeated injections of r-hIL-7 in HIV Patients receiving ART in INSPIRE 2 & 3 trials

Rodolphe Thiebaut[1]; Ana Jarne[1]; Jean-Pierre Routy[2]; Irini Sereti[3]; Margaret A. Fischl[4]; Prudence Ive[5]; Roberto Speck[6]; Giuseppe Tambussi[7]; Yves Lévy[8]; Michael M Lederman[9]
on behalf of Inspire 2 and Inspire 3 study groups

[1]Bordeaux University, Bordeaux, France; [2]McGill University, Montreal, Canada; [3]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US; [4]University of Miami, Miami, FL, US; [5]Wits Health consortium, Johannesburg, South Africa; [6]University Hospital Zurich, Zurich, Switzerland; [7]San Raffaele Scientific Institute, Milano, Italy; [8]INSERM, Paris, France; [9]Case Western Reserve University, Cleveland, OH, US

338 CRF19_cpx Is an Evolutionary Fit HIV-1 Variant Exclusively Associated With Rapid Progression to AIDS in Cuba

Vivian Kouri[2]; Ricardo Khouri[1]; Yoan Alemán[2]; Yeissel Abrahantes[2]; Nico Pfeifer[3]; Andrea-Clemencia Pineda-Peña[4]; Jorge Pérez[2]; Lissette Pérez[2]; Kristel Van Laethem[4]; **Anne-Mieke Vandamme**[4]

[1]Fundação Oswaldo Cruz, Salvador, Brazil; [2]Instituto Pedro Kouri, Havana, Cuba; [3]Max Planck Institute for Informatics, Saarbrucken, Germany; [4]Katholieke Universiteit Leuven, Leuven, Belgium

TUESDAY, FEBRUARY 24, 2015

Session P-E1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

The Effect of HIV Infection on B Cells

339 Acute HIV-1 Infection Is Associated With Rapid Changes in B-Cell Subsets and Levels of CXCL13

Jenniffer K. Maroa[1]; Anne-Sophie Dugust[2]; Zelda Euler[2]; Yathisha Ramlakhan[1]; Krista Dong[3]; Bruce Walker[2]; Thumbi Ndung'u[4]; Galit Alter[2]

[1]University of KwaZulu-Natal, Durban, South Africa; [2]Ragon Institute of MIT, MGH and Harvard, Boston, MA, US; [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [4]HIV Pathogenesis Programme, Durban, South Africa

340 Bone Marrow Plasma Cells Dictate Serum HIV-Specific Antibodies in Chronic Viremia

Jairo Mauricio Montezuma-Rusca[1]; **Olivia R. Fankuchen**[1]; Lela Kardava[1]; Clarisa M. Buckner[1]; Aaron Louie[1]; Yuxing Li[2]; Tae Wook Chun[1]; Katherine R. Calvo[3]; Susan Moir[1]; Anthony S. Fauci[1]

[1]NIAID/NIH, Bethesda, MD, US; [2]University of Maryland, Rockville, MD, US; [3]NIH Clinical Center, Bethesda, MD, US

341 Reduced Expression of Blimp-1 on Memory B Cells in Patients with HIV-1 Infection

Claudia Beisel; Ilona Toth; Jan van Lunzen; Julian Schulze zur Wiesch

University Hospital Hamburg-Eppendorf, Hamburg, Germany

342 Similar or Higher Memory Responses to Influenza Vaccination in Aviremic HIV-infected Patients on Antiretroviral Therapy

Zhenwu Luo; Lisa Martin; J. Michael Kilby; **Wei Jiang**

Medical University of South Carolina, Charleston, SC, US

Session P-E2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

The Envelope/Antibody Dynamic

343 Estimating and Visualizing HIV-1 Susceptibility to Broadly Neutralizing Antibodies

Anna Feldmann; Nico Pfeifer

Max Planck Institute for Informatics, Saarbrücken, Germany

344 Sequential SHIV-Env Clones With Neutralization Sensitivity for Breadth Development

Manxue Jia; Cecilia Cheng-Mayer; Xueling Wu

Aaron Diamond AIDS Research Center, New York, NY, US

345 V1V2 Neutralizing Epitopes Are Conserved Within Divergent Groups of HIV-1

Marion Morgand[1]; Mélanie Bouvin-Pley[1]; Craig S Pace[2]; David Ho[2]; Pascal Poignard[3]; Marie Pancera[4]; Jean-Christophe Plantier[5]; Francois Simon[6]; Martine Braibant[1]; Francis Barin[7]

[1]Université de Tours, Inserm U966, Tours, France; [2]Aaron Diamond AIDS Research Center, The Rockefeller University, New York, NY, US; [3]Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, CA, US; [4]Vaccine Research Center, NIAID, NIH, Bethesda, WA, US; [5]Université de Rouen, CHU Charles Nicolle, Rouen, France; [6]Laboratoire de Virologie, Hôpital St Louis, Paris, France; [7]Université de Tours, Inserm U966, Laboratoire de Bactériologie-Virologie, CNR du VIH, CHU Bretonneau, Tours, France

346 Improving Neutralization Potency and Breadth by Combining Broadly Reactive HIV-1 Antibodies Targeting Major Neutralization Epitopes

Rui Kong[1]; Mark Louder[1]; Kshitij Wagh[2]; Robert Bailer[1]; Kelli Greene[3]; Hongmei Gao[3]; Michel Nussenzweig[4]; Bette Korber[2]; David Montefiori[3]; John Mascola[1]

[1]Vaccine Research Center, NIAID, NIH, Bethesda, MD, US; [2]Los Alamos National Laboratory, Los Alamos, NM, US; [3]Duke University Medical Center, Durham, NC, US; [4]The Rockefeller University, New York, NY, US

347 Improved Antibody Cross-Neutralizing Activity in HIV-1 Dual-Infected LTNP Patients

Maria Pernas[1]; Concepción Casado[1]; Victor Sanchez-Merino[2]; Alberto Sanchez-Merino[2]; Isabel Olivares[1]; eloisa Yuste[2]; Cecilio Lopez-Galíndez[1]

[1]Instituto de Salud Carlos III, Majadahonda, Spain; [2]Institut d'Investigacions Biomediquès, Barcelona, Spain

348 Characterization of CD4 Independent HIV-1 Envelope as Potential Immunogens

Lifei Yang[1]; Bradley Cleveland[1]; Andrea P. Jordan[2]; Patricia Polacino[1]; James A. Hoxie[2]; Shiu-Lok Hu[1]

[1]University of Washington, Seattle, WA, US; [2]University of Pennsylvania, Philadelphia, PA, US

349 Phenotypic Neutralization Sieve Analysis of an SIV Nonhuman Primate Vaccine Challenge Study

Fang-Hua Lee[1]; Brandon F. Keele[3]; Robert Doms[1]; George M. Shaw[1]; Mario Roederer[2]; **Katharine J. Bar**[1]

[1]University of Pennsylvania, Philadelphia, PA, US; [2]Vaccine Research Center, NIAID, NIH, Bethesda, MD, US; [3]National Cancer Institute, Frederick, MD, US

350 AvFc, a Novel Fc Fusion Protein Targeting Env High-Mannose Glycans

Nobuyuki Matoba; Adam Husk; J. Calvin Kouokam; Krystal Hamorsky; Tiffany Grooms-Williams; Garima Mahajan

University of Louisville James Graham Brown Cancer Center, Owensboro, KY, US

351 DARPins as Entry Inhibitor Alternative to HIV-1 Broadly Neutralizing Antibodies

Emanuel Stiegeler; Nikolas Friedrich; Thomas Reinberg; Mylène Morin; Yufan Wu; Jonas V. Schaefer; Peter Rusert; John Robinson; Andreas Plückthun; Alexandra Trkola

University of Zurich, Zurich, Switzerland

WEDNESDAY, FEBRUARY 25, 2015

Session P-E3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

New Approaches to Immunostimulation

352 Use of Pre-ART-Adjusted Endpoints in the Analysis of an HIV Therapeutic Vaccine Trial

Yunda Huang[1]; Lily Zhang[1]; Darren Jolliffe[3]; Arnt-Ove Hovden[4]; Mats Okvist[4]; Pantaleo Giuseppe[2]; Maja A. Sommerfelt[4]

[1]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [2]Lausanne University Hospital, Lausanne, Switzerland; [3]S-cubed Biometrics Ltd, Oxfordshire, United Kingdom; [4]Bionor Pharma ASA, Oslo, Norway

353 Decreased HIV-Specific T-Regulatory Responses Mark Effective Vaccine-Induced Immunity

Vedran Brezar[1]; Nicolas Ruffin[1]; Laura Richert[2]; Mathieu Surenaud[1]; Christine Lacabaratz[1]; Karolina Palucka[3]; Rodolphe Thiebaut[2]; Jacques Banchereau[1]; Yves Lévy[1]; Nabila Seddiki[1]

[1]Inserm U955 (Eq16)-UPEC-VRI, Créteil, France; [2]Univ Bordeaux-ISPED-Inserm U897-VRI, Bordeaux, France; [3]Ralph M. Steinman Center for Cancer Vaccines–Baylor Institute for Immunology Research, Dallas, TX, US

354 Viral Reservoir Dynamics After Therapeutic Vaccination and cART Interruption

Cristina Andres[1]; Carmen Alvarez-Fernandez[1]; Nuria Climent[1]; Teresa Gallart[1]; Montserrat Plana[1]; Agathe Leon[1]; Nicolas Chomont[2]; Jose M. Gatell[1]; **Felipe Garcia**[1]; Sonsoles Sanchez-Palomino[1]

[1]Hospital Clinic, Barcelona, Spain; [2]Vaccine and Gene Therapy Institute, Port St Lucie, FL, US

355 HIV-1 Envelope Epitope Recognition Is Influenced by Immunoglobulin D_H Gene Segment Repertoire

Yuge Wang[2]; Aaron Sanchez-Silva[2]; Barton Haynes[1]; Harry Schroeder[2]

[1]Duke University, Durham, NC, US; [2]University of Alabama at Birmingham, Birmingham, AL, US; [3]University of Alabama at Birmingham, Birmingham, AL, US

356 Human Rhinovirus Displaying HIV-1 4E10 Epitope Elicits Broad Neutralization in hICAM-1 Tg Mice

Guohua Yi[1]; Xiongying Tu[2]; Preeti Bharaj[1]; Premlata Shankar[1]; Manjunath Swamy[1]

[1]Texas Tech University Health Sciences Center, El Paso, TX, US; [2]University of Minnesota, St Paul, MN, US

357 WITHDRAWN

358 A Superagonist Antibody to Human Interleukin-21 Increases HIV-Specific T-Cell Function

Yew Ann Leong[1]; Yanfang Cui[1]; Zhian Chen[1]; Fiona Wightman[1]; Pellegrini Marc[2]; Jamie Rossjohn[1]; Sharon R. Lewin[3]; Alan Landay[4]; Charles Mackay[1]; Di Yu[1]

[1]Monash University/Alfred Hospital, Melbourne, Australia; [2]Walter and Eliza Hall Institution, Melbourne, Australia; [3]University of Melbourne, Melbourne, Australia; [4]Rush University Medical Center, Chicago, IL, US; [5]Monash University/Alfred Hospital, Melbourne, Australia

THURSDAY, FEBRUARY 26, 2015

Session P-E4 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Cellular Immune Response to HIV

359 Evolution of HIV-Specific CD8+ T-Cell Responses in Hyperacute HIV Infection

Zaza M. Ndhlovu[1]; Nikoshia Mewalal[1]; Philomena Kamya[1]; Thandeka Nkosi[1]; Karyn Pretorius[1]; Nasreen Ismail[1]; Amber Moodley[2]; Krista Dong[2]; Thumbi Ndung'u[1]; Bruce Walker[2]

[1]University of KwaZulu-Natal, Durban, South Africa; [2]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, US

360 Nonclassical Regulatory HIV-1–Specific CD8 T Cells in HIV-1 Disease Progression

Selena Vigano[2]; Chun Li[2]; Jordi J. Negron[2]; Bruce D. Walker[2]; Mathias Lichterfeld[1]; Xu G. Yu[2]

[1]Massachusetts General Hospital, Boston, MA, US; [2]The Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, US

361 Nef Plays a Role in the Resistance of SIV-Infected Macrophages to $CD8^+$ T-Cell Suppression

Jennifer N. Rainho; Mauricio A. Martins; Francesc Cunyat; David I. Watkins; Mario Stevenson

University of Miami, Miami, FL, US

362 Defining Efficacious HIV-Specific CTL Responses Using Saporin-Conjugated Tetramers

Ellen M. Leitman[1]; Stuart Sims[2]; Rebecca P. Payne[1]; Fabian Chen[3]; Lynn Riddell[4]; Soren Buus[5]; Steven Deeks[6]; Bruce Walker[7]; Philippa C. Matthews[1]; Philip J. Goulder[1]

[1]University of Oxford, Oxford, United Kingdom; [2]ETH Zurich, Basel, Switzerland; [3]Royal Berkshire Hospital, Reading, United Kingdom; [4]Northamptonshire Healthcare NHS Trust, Northampton, United Kingdom; [5]University of Copenhagen, Copenhagen, Denmark; [6]University of California San Francisco, San Francisco, CA, US; [7]Ragon Institute of MGH, MIT and Harvard, Charlestown, MA, US

363 Linking Pig-Tailed Macaque Major Histocompatibility Complex Class I Haplotypes and Cytotoxic T Lymphocyte Escape Mutations in SIV Infection

Shayarana Gooneratne[1]; Hamid Alinejad-Rokny[2]; Diako Ebrahimi Mohammadi[2]; Patrick Bohn[3]; Roger Wiseman[3]; David O'Connor[3]; Miles Davenport[2]; Stephen Kent[1]

[1]University of Melbourne, Melbourne, Australia; [2]University of New South Wales, Kensington, Australia; [3]University of Wisconsin Madison, Madison, WI, US

364 HLA Class-II–Associated HIV Polymorphisms Predict Escape From CD4 T-Cell Responses

Nathaniel B. Erdmann[1]; Victor Du[1]; Jonathan M. Carlson[2]; John Sidney[3]; Ling Yue[4]; Susan Allen[4]; Eric Hunter[4]; Sonya L. Heath[1]; Anju Bansal[1]; Paul A. Goepfert[1]

[1]University of Alabama at Birmingham, Birmingham, AL, US; [2]Microsoft Research, Los Angeles, CA, US; [3]La Jolla Institute of Allergy and Immunology, La Jolla, CA, US; [4]Emory University, Atlanta, GA, US

365 Rapid Construction of HIV-1-Specific T Cell Receptor Gene Therapy Lentiviral Vectors

Christian Hofmann; Christian-Raul Aguilera-Sandoval; Arumugam Balamurugan; Priya Patel; Brian Diep; Edward Martin; Sangeun Park; Diana Y. Chen; Hwee Ng; Otto O. Yang

University of California Los Angeles, Los Angeles, CA, US

366 The Role of Exosomes in Semen in Suppressing Natural and Vaccine-Induced Immunity

Lucia Vojtech; Sean Hughes; Claire Levy; Florian Hladik

University of Washington, Seattle, WA, US

367 IFN-alpha Stimulated NK Lysis of HIV-Infected $CD4^+$ T Cells Requires NKp46 and NKG2D

Costin Tomescu[1]; Domenico Mavilio[2]; Luis J. Montaner[1]

[1]The Wistar Institute, Philadelphia, PA, US; [2]Humanitas Clinical and Research Center, Milan, Italy

TUESDAY, FEBRUARY 24, 2015

Session P-F1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Immune-Based Strategies in Latency

368 Stimulation of Broad CTL Response Is Required to Clear Latent HIV-1 in Humanized Mice

Liang Shan[1]; Kai Deng[2]; Richard Flavell[1]; Robert F. Siliciano[2]

[1]Yale University, New Haven, CT, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US

369 *In vivo* effects of Panobinostat and Romidepsin on HIV-1-specific CD8 T Cell Immunity

Rikke Olesen[1]; Thomas A. Rasmussen[1]; Mathias Lichterfeld[2]; Mette E. Graversen[1]; Steffen Leth[1]; Lars Østergaard[1]; Ole S. Søgaard[1]; Martin Tolstrup[1]

[1]Aarhus University Hospital, Aarhus, Denmark; [2]Ragon Institute of MIT, MGH and Harvard, Boston, MA, US

370 Vaccine Induced Follicular CD8 T Cells Enhance Control of Pathogenic SIV Infection

Geetha H. Mylvaganam; Daniel Rios; Gregory Tharp; Steven Bosinger; Vijayakumar Velu; Rama R. Amara

Emory University, Atlanta, GA, US

371 Blockade of PD-L1 Does Not Reverse HIV Latency in CD4+ T Cells Ex Vivo

Elizabeth Fyne[1]; Shalyn Campellone[2]; Huilin Qi[2]; Amy Sheaffer[2]; Stephen Mason[2]; John W. Mellors[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]Bristol-Myers Squibb Co., Wallingford, CT, US

372 Impact of HIV Latency Reversing Agents on Natural Killer Cells

Carolina Garrido; Julia Sung; Swati Gupta; Katherine Sholtis; Nancie Archin; David Margolis Medicine, University of North Carolina

University of North Carolina, Chapel Hill, NC, US

THURSDAY, FEBRUARY 26, 2015

Session P-F2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Viral Reservoir Dynamics During ART

373 The Earlier cART Is Initiated During PHI, the More Intracellular HIV-DNA Decreases

Moussa Laanani[2]; Jade Ghosn[1]; Asma Essat[2]; Adeline Mélard[3]; Rémonie Seng[2]; Emmanuel Mortier[4]; Cécile Goujard[2]; Laurence Meyer[2]; Christine Rouzioux[3]
On behalf of the ANRS PRIMO Cohort Study Group

[1]APHP, Hôtel Dieu University Hospital, Paris, France; [2]APHP, Bicêtre Hospital, Le Kremlin-Bicêtre, France; [3]APHP, Necker Hospital, Paris, France; [4]APHP, Louis Mourier Hospital, Colombes, France

374 Decay Rate and HIV-1 DNA Reservoir Size Following Early Infant Antiretroviral Therapy

Priyanka Uprety[1]; Kaitlin Rainwater-Lovett[2]; Ellen G. Chadwick[3]; Edmund Capparelli[4]; Carrie Ziemniak[2]; Katherine Luzuriaga[5]; Larry Moulton[1]; Deborah Persaud[2]
International Maternal Pediatric Adolescent AIDS Clinical Trial Network (IMPAACT) P1030 trial group

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [4]University of California San Diego, San Diego, CA, US; [5]University of Massachusetts Medical School, Boston, MA, US

375 Detectable CMV in PBMC Is Associated With Slower HIV DNA Decay During Suppressive ART

Sara Gianella Weibel; Christy Anderson; Susanna R. Var; Michelli Faria de Oliveira; Marta Massanella; Susan J. Little; Douglas D. Richman; Matt Strain; Josue Pérez-Santiago; David M. Smith

University of California San Diego, La Jolla, CA, US

376 Stable Total HIV-1 DNA Levels Prior and Post ART Interruption in Chronic HIV

Emmanouil Papasavvas[1]; Matthew Strain[2]; Steven Lada[2]; Jocelin Joseph[1]; Livio Azzoni[1]; Karam Mounzer[3]; Jay R. Kostman[4]; Douglas D. Richman[2]; Luis J. Montaner[1]

[1]The Wistar Institute, Philadelphia, PA, US; [2]VA San Diego Healthcare System and the University of California, San Diego, CA, US; [3]Jonathan Lax Immune Disorders Treatment Center, Philadelphia Field Initiating Group for HIV-1 Trials, Philadelphia, PA, US; [4]Presbyterian Hospital–University of Pennsylvania Hospital, Philadelphia, PA, US

377 Aviremia 10-Year Post-ART Discontinuation Initiated at Seroconversion

Sabine I. Kinloch[1]; Lucy Dorrell[2]; Hongbing Yang[2]; Linos Vandekerckhove[3]; Ward de Spiegelaere[3]; Eva Malatinkova[3]; Sabine Yerly[4]; Daniel Webster[5]; Margaret Johnson[5]

[1]University College London, London, United Kingdom; [2]University of Oxford, Oxford, United Kingdom; [3]Universitair Ziehenhuis Gent, Gent, Belgium; [4]Geneva University Hospital, Geneva, Switzerland; [5]Royal Free London NHS Foundation Trust, London, United Kingdom

378 Identifying HIV Variants that Rebound after Treatment Interruption

Mary F. Kearney[2]; Wei Shao[3]; Rajesh T. Gandhi[4]; Brandon F. Keele[3]; **Jonathan Z. Li**[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [2]National Cancer Institute (NCI), Frederick, MD, US; [3]Frederick National Laboratories for Cancer Research, Frederick, MD, US; [4]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

379 Characterizing the Active HIV Reservoir on ART: Cell-Associated HIV RNA and Viremia

Feiyu Hong; Elizabeth Fyne; Anthony R. Cillo; Margaret A. Bedison; Dianna Koontz; John W. Mellors

University of Pittsburgh, Pittsburgh, PA, US

380 Liver Macrophages and HIV-1 Persistence

Abraham J. Kandathil; Christine M. Durand; Jeffrey Quinn; Andrew Cameron; David L. Thomas; Ashwin Balagopal

Johns Hopkins School of Medicine, Baltimore, MD, US

381 Large-Scale Analysis of HIV-1 Integration Sites in Untreated and Treated Patients

Stephanie Laufs[1]; **Diana Schenkwein**[1]; Neeltje Kootstra[2]; Frank A. Giordano[5]; Christoph Stephan[3]; Hans-Georg Kraeusslich[4]; Winfried Kern[6]; Susanne Usadel[6]; Manfred Schmidt[1]; Christof von Kalle[1]

[1]National Center for Tumor Diseases; German Cancer Research Center, Heidelberg, Germany; [2]Sanquin Research, Landsteiner Laboratory, and Center for Infectious Diseases and Immunity Amsterdam, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; [3]University Hospital Frankfurt, Frankfurt, Germany; [4]Department of Infectious Diseases, Virology, University Hospital Heidelberg, Heidelberg, Germany; [5]Heidelberg University, Heidelberg, Germany; [6]Division of Infectious Diseases, Department of Medicine, Albert-Ludwigs-University Center for Infectious Diseases & Travel Medicine, and IFB-Center for Chronic Immunodeficiency, University Hospital, Freiburg, Germany

382 Identical Sequence Expansions Are Predominantly Found in Effector Memory T Cells

Susanne von Stockenstrom[1]; Eunok Lee[2]; Lina Odevall[1]; Elizabeth Sinclair[3]; Hiroyu Hatano[3]; Peter Bacchetti[4]; Peter W. Hunt[3]; Steven G. Deeks[3]; Frederick M. Hecht[3]; Sarah E. Palmer[2]

[1]Karolinska Institutet, Stockholm, Sweden; [2]Westmead Millenium Institute and University of Sydney, Sydney, Australia; [3]Department of Medicine, University of California San Francisco, San Francisco, CA, US; [4]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, US

383 Long-Term Effect of Temporary ART During Primary HIV Infection on the Viral Reservoir

Alexander Pasternak[1]; Jan Prins[2]; Ben Berkhout[1]

[1]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [2]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands

Session P-F3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Cellular Factors of Latency

384 Minor Contribution of Host-HIV Readthrough Transcripts to the Level of HIV-1 *gag* RNA

Alexander Pasternak[1]; Una O'Doherty[2]; Ben Berkhout[1]

[1]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [2]University of Pennsylvania, Philadelphia, PA, US

385 MicroRNA-155 Reinforces HIV Latency by Downregulating the TRIM32 Viral Activator

Debbie S. Ruelas[2]; Jonathan Chan[2]; Eugene Oh[1]; Amy Heidersbach[2]; Andrew Hebbeler[2]; Leonard Chavez[2]; Eric Verdin[2]; Warner C. Greene[2]

[1]University of California San Francisco (UCSF), San Francisco, CA, US; [2]University of California Berkeley, Berkeley, CA, US

386 Select Host Restriction Factors Are Associated With HIV Persistence During Therapy

Mohamed Abdel-Mohsen[1]; Leonard Chavez[1]; Charlene Wang[1]; Matt Strain[2]; Xutao Deng[1]; Christopher D. Pilcher[3]; Teri Liegler[3]; Douglas D. Richman[2]; Steven Deeks[3]; Satish Pillai[1]

[1]Blood Systems Research Institute, San Francisco, CA, US; [2]University of California San Diego, La Jolla, CA, US; [3]University of California San Francisco, San Francisco, CA, US

387 Selectively Eliminating HIV Latently Infected Cells Without Viral Reactivation

Grant R. Campbell; Rachel S. Bruckman; Yen-Lin Chu; Stephen A. Spector

University of California San Diego, La Jolla, CA, US

388 PD1 Identifies Latently HIV-Infected Nonproliferating and Proliferating CD4+ T Cells

Renee M. van der Sluis[1]; Nitasha A. Kumar[1]; Vanessa A. Evans[1]; Rafick P. Sekaly[2]; Remi Fromentin[2]; Nicolas Chomont[2]; Paul U. Cameron[1]; Sharon R. Lewin[1]

[1]Doherty Institute, Melbourne University, Melbourne, Australia; [2]VGTI-Vaccine and Gene Therapy Institute Florida, Port St. Lucie, FL, US

389LB 2B4+PD1+ Naïve and Memory CD4+ T Cells Are Associated With Residual Viremia on ART

Cynitha Klamar; Feiyu Hong; John Bui; Anthony R. Cillo; Arcadio Agudelo-Hernandez; Deborah A. McMahon; Charles R. Rinaldo; John W. Mellors; **Bernard J. Macatangay**

University of Pittsburgh, Pittsburgh, PA, US

390 Nascent LTR-Driven Transcription Can Lead to Translation of HIV Proteins in Resting CD4+ T Cells

Laura DeMaster[1]; Alexander Pasternak[2]; Una O'Doherty[1]

[1]University of Pennsylvania, Philadelphia, PA, US; [2]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands

WEDNESDAY, FEBRUARY 25, 2015

Session P-F4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Dynamics of Latency and Reactivation

391 Influenza Vaccination Increases HIV-1 Transcription During Antiretroviral Therapy

Christina C. Yek[1]; Sara Gianella[1]; Montserrat Plana[2]; Pedro Castro[2]; Felipe Garcia[2]; Marta Massanella[1]; David M. Smith[1]

[1]University of California San Diego, San Diego, CA, US; [2]University of Barcelona, Barcelona, Spain

392 Defective HIV-1 Proviruses Can Be Transcribed Upon Activation

Ya-Chi Ho; Ross Pollack; Patrick Yong; Robert F. Siliciano

Johns Hopkins University School of Medicine, Baltimore, MD, US

393 Kinetics of HIV-1 Gene Expression Following Reactivation in a Primary Cell Model of Latency

Victoria Walker-Sperling; Joel Blankson

Johns Hopkins University School of Medicine, Baltimore, MD, US

394 Variable HIV Replication Competency Following Latency Disruption in CD4+ T Cells

Jason M. Hataye; Joseph Casazza; David Ambrozak; Eli Boritz; Takuya Yamamoto; Daniel Douek; Richard A. Koup

National Institute of Allergy and Infectious Diseases, Bethesda, MD, US

395 Latent HIV-1 Reactivation and Lysosomal Destabilization Synergize to Host Cell Death

Metodi Stankov[1]; Christina Suhr[1]; Hazel Lin[1]; Diana Panayotova-Dimitrova[2]; Christine Goffinet[1]; Georg Behrens[1]

[1]Hannover Medical School, Hannover, Germany; [2]Mannheim Clinic of University of Heidelberg, Mannheim, Germany

396 Noninduced Proviral Genome Characterization in Perinatal HIV Infection

Kaitlin Rainwater-Lovett[1]; Carrie Ziemniak[1]; Douglas Watson[2]; Katherine Luzuriaga[3]; Priyanka Uprety[4]; Yahui Chen[1]; Ya-Chi Ho[1]; Deborah Persaud[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]University of Maryland, Baltimore, MD, US; [3]University of Massachusetts Medical School, Worcester, MA, US; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]Johns Hopkins University School of Medicine, Baltimore, MD, US

397 Multiple Rounds of T-Cell Activation Induce Additional HIV-1 From the Latent Reservoir

Nina N. Hosmane; Adam A. Capoferri; Robert F. Siliciano

Johns Hopkins University School of Medicine, Baltimore, MD, US

398 The Inducible HIV-1 Reservoir Predicted by Combinations of pre- and on-ART Parameters

Anthony R. Cillo; Michele Sobolowski; Elizabeth Fyne; Dianna Koontz; Feiyu Hong; John W. Mellors

University of Pittsburgh, Pittsburgh, PA, US

399 Effects of Antineoplastic Chemotherapy on Dynamics of HIV Population Genetics In Vivo

Sarah A. Watters[1]; Wei Shao[1]; Kieron Dunleavy[3]; Margaret Shovlin[3]; Mark N. Polizzotto[3]; Thomas S. Uldrick[3]; Robert Yarchoan[3]; Wyndham Wilson[3]; Frank Maldarelli[1]

[1]National Cancer Institute (NCI), Frederick, MD, US; [2]National Cancer Institute (NCI), Frederick, MD, US; [3]National Cancer Institute (NCI), Bethesda, MD, US; [4]National Cancer Institute (NCI), Bethesda, MD, US; [5]National Cancer Institute (NCI), Bethesda, MD, US; [6]National Cancer Institute (NCI), Bethesda, MD, US

Session P-F5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Gene Editing

400 Targeted Disruption of Essential HIV-1 Proviral Genes by Rare-Cutting Endonucleases

Harshana S. De Silva Feelixge; Nixon Niyonzima; Harlan L. Pietz; Martine Aubert; Dan Stone; **Keith R. Jerome**

Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US

401 Enhancing Anti-HIV Gene Therapy: Combining MegaTAL Nuclease Gene Editing With Selection Cassettes

Biswajit Paul[2]; Alexander Astrakhan[3]; Patrick Younan[2]; Blythe D. Sather[4]; Jordan Jarjour[3]; Guillermo Romano[2]; John P. Kowalski[2]; Iram Khan[4]; David J. Rawlings[4]; Hans-Peter Kiem[2]

[1]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [3]BluebirdBio, Cambridge, MA, US; [4]Seattle Children's Research Institute, Seattle, WA, US

402 A Phase I Clinical Trial of Autologous CD4+ T Cells Modified With a Retroviral Vector Expressing the MazF Endoribonuclease in Patients With HIV-1

Jeffrey M. Jacobson[1]; Hideto Chono[2]; Meghan Metz[1]; Gabriela Plesa[3]; Julie Jadlowsky[3]; Simon Lacey[3]; Bruce Levine[3]; Hirofumi Yoshioka[2]; Junichi Minemo[2]; Carl H. June[3]

[1]Drexel University College of Medicine, Philadelphia, PA, US; [2]Takara Bio Inc., Shiga, Japan; [3]University of Pennsylvania, Philadelphia, PA, US

403 CRISPRs Are Able to Efficiently Target Latent HIV and Halt New Infections

Robert Jan Lebbink; Dorien de Jong; Femke Wolters; Emmanuel J. Wiertz; **Monique Nijhuis**

University Medical Center Utrecht, Utrecht, Netherlands

TUESDAY, FEBRUARY 24, 2015

Session P-F6 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HDAC Inhibitors

404 Histone Deacetylase (HDAC) and Histone Acetyltransferase (HAT) Inhibitors Have Opposing Effects on Cellular Susceptibility to HIV Infection

Mark B. Lucera[2]; Curtis Dobrowolski[1]; Jonathan Karn[1]; John C. Tilton[2]

[1]Case Western Reserve University, Cleveland Heights, OH, US; [2]Case Western Reserve University, Cleveland, OH, US

405 Panobinostat Dosing Has Broad but Transient Immunomodulatory Effects in HIV Patients

Martin Tolstrup[1]; Christel R. Brinkmann[1]; Thomas A. Rasmussen[1]; Rikke Olesen[1]; Anne Sofie Kjær[1]; Mathias Lichterfeld[2]; Charles Dinarello[3]; Lars Østergaard[1]; Ole S. Søgaard[1]

[1]Aarhus University Hospital, Aarhus, Denmark; [2]Ragon Institute of MIT, MGH and Harvard, Boston, MA, US; [3]University of Colorado, Denver, CO, US

406 Multi-Dose Romidepsin in SIV-Infected RMs Reactivates Latent Virus in Absence of ART

Benjamin Policicchio[1]; Egidio Brocca-Cofano[1]; Cuiling Xu[1]; Dongzhu Ma[1]; Hui Li[2]; George Richter-Haret[1]; Tammy Dunsmore[1]; George M. Shaw[2]; Ivona Pandrea[1]; Cristian Apetrei[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]University of Pennsylvania, Philadelphia, PA, US

407 Suberanilohydroxamic Acid (SAHA)-Induced Histone Modifications in the HIV Promoter in a Human, Primary CD4 T Cell Model of Latency

Brian Reardon[1]; Amey Mukim[2]; Savitha Deshmukh[2]; Christopher H. Woelk[3]; Douglas D. Richman[1]; Celsa A. Spina[1]

[1]University of California San Diego, La Jolla, CA, US; [2]VA San Diego Healthcare System, La Jolla, CA, US; [3]University of Southampton, Southampton, United Kingdom

408 Donor-to-Donor Variation in the Host Gene Expression Response to SAHA

Bastiaan Moesker[1]; Brian Reardon[2]; Nadejda Beliakova-Bethell[2]; Akul Singhania[1]; Michael S. Breen[1]; Christopher H. Woelk[1]

[1]University of Southampton, Southampton, United Kingdom; [2]University of California San Diego, La Jolla, CA, US

409 Off-Target Effects of SAHA May Inhibit HIV Activation

Cory H. White[1]; Harvey E. Johnston[2]; Antigoni Manousopoulou[2]; Celsa A. Spina[1]; Douglas D. Richman[1]; Spiros D. Garbis[2]; Christopher H. Woelk[2]; Nadejda Beliakova-Bethell[1]

[1]University of California San Diego, La Jolla, CA, US; [2]University of Southampton, Southampton, United Kingdom

410 Bystander Effect of Histone Deacetylase Inhibitors on HIV-1 Infection

Grant R. Campbell; Rachel S. Bruckman; Yen-Lin Chu; Stephen A. Spector

University of California San Diego, La Jolla, CA, US

411 HIV-1 Reactivation Increases Mitochondrial Priming of the Latent Reservoir

Jeremy A. Ryan[2]; Allison L. Schure[1]; Zelda Euler[3]; Anthony Letai[2]; **Athe Tsibris**[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, US; [2]Dana-Farber Cancer Institute, Boston, MA, US; [3]Ragon Institute of MIT, MGH and Harvard, Cambridge, MA, US

Session P-F7 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Pharmacologic Latency-Reactivation Agents

412 Reactivation of HIV Latently Infected T Cells by Targeting Tat IRES Translation

Georges Khoury[1]; Sri Ramarathinam[2]; Charlene Mackenzie[1]; David Yurick[1]; Con Sonza[1]; Tony Purcell[2]; Damian F. Purcell[1]

[1]University of Melbourne At the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia; [2]Monash University/Alfred Hospital, Melbourne, Australia

413 Targeting HIV-1 Latency With a Potent Tat Inhibitor

Guillaume Mousseau[1]; Remi Fromentin[2]; Cari Kessing[2]; Lydie Trautmann[2]; Nicolas Chomont[2]; **Susana T. Valente**[1]

[1]The Scripps Reasearch institute, Jupiter, FL, US; [2]The Vaccine and Gene Therapy Institute, Port Saint Lucie, FL, US

414 Impact of IFNα-2a on the Replication-Competent HIV-1 Reservoir in CD4+ T Cells

Sara Morón-López[2]; Maria Salgado[2]; Dan Ouchi[2]; Mari Carmen Puertas[2]; Toni Jou[3]; Cristina Tural[3]; Jordi Navarro[1]; Mercedes Perez-Bernal[1]; **Manel Crespo**[1]; Javier Martínez-Picado[2]

[1]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [2]AIDS Research Institute irsiCaixa, Barcelona, Spain; [3]Fundació Lluita contra la SIDA, Barcelona, Spain

415 Immune Modulation With Rapamycin as a Potential Strategy for HIV-1 Eradication

Alyssa R. Martin; Robert F. Siliciano

Johns Hopkins University School of Medicine, Baltimore, MD, US

416 Latency Reversing Agents Activate Latent Reservoirs in the Brain of SIV-Infected Macaques

Lucio Gama[1]; Sarah Price[1]; Erin Shirk[1]; Suzanne E. Queen[1]; Ming Li[1]; Brandon Bullock[1]; Stephen Wietgrefe[2]; Luiz Pianowski[3]; M. Christine Zink[1]; Janice Clements[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]University of Minnesota, Minneapolis, MN, US; [3]Bioqual, Valinhos, Brazil

417 TLR7 Agonist GS-9620 Activates HIV-1 in PBMCs From HIV-Infected Patients on cART

Derek D. Sloan[1]; Alivelu Irrinki[1]; Angela Tsai[1]; Jasmine Kaur[1]; Jay Lalezari[2]; Jeff Murry[1]; Tomas Cihlar[1]

[1]Gilead Sciences, Inc., Foster City, CA, US; [2]Quest Clinical Research, San Francisco, CA, US

418 Baracitinib, Ruxolitinib, Dasatinib Block HIV Replication, Activation, Reactivation

Christina Gavegnano

Emory University, Atlanta, GA, US

419 Ex Vivo Identification of Highly Effective Latency-Reversing Drug Combinations

Gregory M. Laird[1]; C Korin Bullen[1]; Daniel I. Rosenbloom[2]; Alyssa R. Martin[1]; Alison L. Hill[3]; Christine M. Durand[1]; Janet D. Siliciano[1]; Robert F. Siliciano[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Columbia University, New York, NY, US; [3]Harvard University, Boston, MA, US

WEDNESDAY, FEBRUARY 25, 2015

Session P-F8 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Latency Models and Assays

420 Investigating Mechanisms of HIV Persistence Using Droplet Digital PCR Approaches

Elizabeth M. Anderson[1]; Robert Gorelick[2]; Shawn Hill[1]; Catherine A. Rhem[5]; Mary Kearney[1]; John W. Mellors[3]; John M. Coffin[4]; Mike Piatak[2]; Frank Maldarelli[1]

[1]National Cancer Institute at Frederick, Frederick, MD, US; [2]Leidos Biomedical Research, Inc, Frederick, MD, US; [3]University of Pittsburgh, Pittsburgh, PA, US; [4]Tufts University, Boston, MA, US; [5]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

421LB High-Throughput Single-Cell Quantification of HDACi-Based HIV Reservoir Reactivation

Robert W. Yucha[1]; Emily Hanhauser[2]; Kristen S. Hobbs[2]; Helen Bae[3]; Fatih Inci[4]; Hadi Shafiee[2]; Shuqi Wang[4]; Daniel Kuritzkes[1]; Utkan Demirci[4]; Timothy J. Henrich[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, US; [2]Brigham and Women's Hospital, Cambridge, MA, US; [3]Harvard University, Cambridge, MA, US; [4]Stanford University, Palo Alto, CA, US

422 Evaluation of HIV-1 Latency-Reversing Agents by a Modified Virus Growth Assay (VOA)

Riddhima Banga; Francesco Procopio; Matthias Cavassini; Alessandra Noto; Song Ding; Giuseppe Pantaleo; **Matthieu Perreau**

Lausanne University Hospital, Epalinges, Switzerland

423 "Kick and Kill" of Latent HIV-1 Infection in Naïve and Central Memory CD4+ T cells

Jennifer M. Zerbato; Nicolas Sluis-Cremer

University of Pittsburgh, Pittsburgh, PA, US

424 HIV Recombination in the In Vitro T_{CM} Latency Model – Reasons and Solutions

Pawel Bonczkowski[2]; Laura J. Martins[1]; Ward de Spiegelaere[2]; Alberto Bosque[1]; Eva Malatinkova[2]; Christopher H. Woelk[3]; Cory H. White[4]; Adam M. Spivak[5]; Vicente Planelles[1]; Linos Vandekerckhove[2]

[1]University Of Utah School of Medicine, Salt Lake City, UT, US; [2]Ghent University and University Hospital, Ghent, Belgium; [3]University of Southampton, Southampton, United Kingdom; [4]University of California San Diego (UCSD), La Jolla, CA, US; [5]Utah University Hospital, Salt Lake City, UT, US

425 CD4+ Tissue-Resident Memory T Cells Are an Important Reservoir for HIV Persistence

Angela R. Wahl; J. Victor Garcia

University of North Carolina, Chapel Hill, NC, US

426 HIV-1 Reprograms Resting CD4 T Cells via Foxo1 and L-Selectin Suppression

Benjamin Trinité[1]; Chi N. Chan[1]; Caroline S. Lee[1]; Joy Folkvord[2]; Elizabeth Connick[2]; **David N Levy**[1]

[1]New York University, New York, NY, US; [2]University of Colorado Anschutz Medical Campus, Aurora, CO, US

427 Measurements of Viral Transcription in Elite Suppressor CD4+ T Cells

Christopher W. Pohlmeyer; C. Korin Bullen; Greg Laird; Alyssa R. Martin; Victoria Walker-Sperling; Stanley U. Chioma; Robert F. Siliciano; Joel Blankson

Johns Hopkins University School of Medicine, Baltimore, MD, US

428LB Short-Term Disulfiram to Reverse Latent HIV Infection: A Dose Escalation Study

Julian H. Elliott[1]; James H. McMahon[1]; Wendy Hartogensis[2]; Namandje Bumpus[3]; Christina Chang[4]; Sulggi A. Lee[2]; Jeff Lifson[5]; Peter Bacchetti[2]; Steven Deeks[2]; Sharon R. Lewin[4]
on behalf of the Disulfiram Study investigators

[1]Monash University/Alfred Hospital, Melbourne, Australia; [2]University of California San Francisco, San Francisco, CA, US; [3]Johns Hopkins University, Baltimore, MD, US; [4]University of Melbourne, Melbourne, Australia; [5]National Cancer Institute, Frederick, MD, US

Session P-F9 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Stem Cell Transplantation

429 Impact of Combination of Chemotherapy and Autologous Hematopoietic Stem-Cell Transplantation for Lymphoma on HIV Reservoir Persistence

Heloise Delagreverie; laurence Gerard; Marie Laure Chaix; Marie Laure Nere; Lionel Galicier; Francois Simon; Eric Oksendenhendler; Constance Delaugerre

Hôpital Saint-Louis, APHP, Université Paris Diderot, Paris, France

430 HIV-1 Reservoirs and Humoral Immunity in Allogeneic Stem Cell Transplantation Patients

Kathryn E. Stephenson[1]; George H. Neubauer[1]; Emily Hanhauser[2]; Marcelo J. Wolff[3]; Cristian Carvallo[3]; Francisco M. Marty[4]; Steven G. Deeks[5]; Daniel R. Kuritzkes[6]; Dan H. Barouch[1]; Timothy J. Henrich[6]

[1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US; [2]Brigham and Women's Hospital, Boston, MA, US; [3]Clinica Santa Maria, Santiago, Chile; [4]Dana-Farber Cancer Institute, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [5]University of California San Francisco (UCSF), San Francisco, CA, US; [6]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US

431 Breakthrough of Preexisting X4-Capable HIV After Allogeneic Stem-Cell Transplantation

Jens Verheyen[1]; Alexander Thielen[2]; Miriam Dirks[1]; Nadine Lübke[3]; Marek Widera[1]; Lambros Kordelas[1]; Martin Däumer[2]; Rolf Kaiser[3]; Stefan Esser[1]

[1]University Hospital Essen, University Duisburg-Essen, Essen, Germany; [2]Institute of Immunology and Genetics, Kaiserslautern, Germany; [3]University of Cologne, Cologne, Germany; [4]University Hospital Essen, University Duisburg-Essen, Essen, Germany; [5]University Hospital Essen, University Duisburg-Essen, Essen, Germany

432 Allogeneic Transplantation With CCR5 Δ32/Δ32 Cord Blood Hematopoietic Cells in an HIV-1-Infected Patient

Rafael Duarte[1]; **Maria Salgado**[2]; Isabel Sanchez-Ortega[1]; Sara Morón-López[2]; Maria C. Puertas[2]; Lawrenze D. Petz[4]; Sergi Querol[3]; Bonaventura Clotet[2]; Javier Martínez-Picado[2]

[1]Institut Català d'Oncologia, L'Hospitalet del Llobregat, Spain; [2]IrsiCaixa Institute for AIDS Research, Badalona, Spain; [3]Barcelona Cord Blood Bank, Barcelona, Spain; [4]StemCyte International Cord Blood Center, Covina, CA, US

433 CCR5 Editing in Hematopoietic Stem Cells in a Nonhuman Primate Model of HIV/AIDS

Christopher W. Peterson[1]; Jianbin Wang[2]; Patricia Polacino[3]; Michael C. Holmes[2]; Shiu-Lok Hu[3]; Philip D. Gregory[2]; Hans-Peter Kiem[1]

[1]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [2]Sangamo BioSciences, Inc., Richmond, CA, US; [3]University of Washington, Seattle, WA, US

434 Cytoxan Enhancement of SB-728-T Engraftment: A Strategy to Improve Anti-HIV Response

Gary Blick[2]; Jay Lalezari[3]; Ricky Hsu[4]; Erin DeJesus[5]; Trevor Hawkins[6]; Ronald T. Mitsuyasu[7]; Shelley Wang[1]; Gary Lee[1]; **Winson Tang**[1]; Dale Ando[1]

[1]Sangamo BioSciences, Inc., Richmond, CA, US; [2]CIRCLE CARE Center, Norwalk, CT, US; [3]Quest Clinical Research, San Francisco, CA, US; [4]New York University School of Medicine, New York, NY, US; [5]Orlando Immunology Center, Orlando, FL, US; [6]Southwest Care Center, Santa Fe, NM, US; [7]University of California Los Angeles CARE Center, Los Angeles, CA, US

TUESDAY, FEBRUARY 24, 2015

Session P-G1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

CNS Reservoirs

435 Highly Precise Measurements of HIV DNA in CSF and Blood by Droplet Digital PCR

Michelli Faria de Oliveira[1]; Sara Gianella[1]; Scott Letendre[2]; Konrad Scheffler[1]; Sergei L. Kosakovsky Pond[1]; Davey M. Smith[1]; Matt Strain[1]; Ronald J. Ellis[2]

[1]University of California San Diego, La Jolla, CA, US; [2]HIV Neurobehavioral Research Center, San Diego, CA, US

436 Antiretroviral Concentrations in Brain Tissue Are Similar to or Exceed Those in CSF.

Namandjé Bumpus[2]; Qing Ma[4]; David J. Moore[1]; Brookie M. Best[1]; Ronald J. Ellis[1]; Cristian L. Achim[1]; Melanie Crescini[1]; Courtney Fletcher[3]; Igor Grant[1]; **Scott Letendre**[1]
The CNTN Group

[1]University of California San Diego, San Diego, CA, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]University of Nebraska Medical Center, Omaha, NE, US; [4]University at Buffalo, Buffalo, NY, US

437 HIV DNA Peripheral Reservoirs Have a Nonlinear Impact on Brain Pathology

William Hey-Cunningham[2]; Nadene Dermody[3]; Phillip Chan[4]; Bruce Brew[5]; Kersten Koelsch[2]; **Lucette A. Cysique**[1]

[1]NeuRA, University of New South Wales, Randwick, Australia; [2]Kirby Institute, University of New South Wales, Sydney, Australia; [3]Macquarie University, Sydney, Australia; [4]Queen Elizabeth Hospital, HKSAR, Hong Kong, China; [5]St. Vincent's Hospital, University of New South Wales, Sydney, Australia

438 Acute HIV CSF/Plasma RNA Ratios Are Variable and Greater Than in Chronic HIV

Joanna Hellmuth[1]; Serena Spudich[2]; Eugene Kroon[3]; Naponpon Sailasuta[4]; Somprartthana Rattanamanee[3]; Sukalaya Lerdlum[5]; Linda L. Jagodzinski[6]; Shelly J. Krebs[7]; Jintanat Ananworanich[8]; **Victor G. Valcour**[1]
The RV254/SEARCH010 Study Group

[1]University of California San Francisco, San Francisco, CA, US; [2]Yale University School of Medicine, New Haven, CT, US; [3]Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [4]University of Hawaii, Honolulu, HI, US; [5]Chulalongkorn University, Bangkok, Thailand; [6]Walter Reed Army Institute of Research, Silver Spring, MD, US; [7]Henry M. Jackson Foundation for the Advancement of Military Medicine, Silver Spring, MD, US; [8]US Military HIV Research Program, Bethesda, MD, US

439 Greater CSF HIV Reduction and CSF Rapid Decay Associated with Improved Neurocognition

Kevin R. Robertson[1]; Natalie M. Bowman[1]; Sarah B. Joseph[1]; Prema Menezes[1]; Nisha Bhatia[2]; Christopher Lippincott[1]; Michael Vinikoor[1]; Joseph Eron[1]; Ronald Swanstrom[1]; Richard Price[2]
THINC UNC

[1]University of North Carolina, Chapel Hill, Chapel Hill, NC, US; [2]University of California San Francisco, San Francisco, CA, US

440 HIV-1 Replication in the CNS Is Associated With Increased Neurocognitive Impairment

Sarah B. Joseph[1]; Laura Kincer[1]; Natalie M. Bowman[1]; Prema Menezes[1]; Kevin Robertson[1]; Albert M. Anderson[2]; David W. Loring[3]; Joseph J. Eron[1]; Richard W. Price[4]; Ronald Swanstrom[1]

[1]University of North Carolina, Chapel Hill, Chapel Hill, NC, US; [2]Emory University, Atlanta, GA, US; [3]Emory University, Atlanta, GA, US; [4]University of California San Francisco, San Francisco, CA, US; [5]University of North Carolina, Chapel Hill, Chapel Hill,, NC, US

Session P-G2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Optimizing ART for HAND Treatment and Prevention

441 Maraviroc-Enhanced CART Improves Cognition in Virally Suppressed HAND: A Pilot Study

Thomas M. Gates[1]; Lucette A. Cysique[2]; Joga Chaganti[1]; Krista J. Siefried[1]; **Bruce J. Brew**[1]

[1]St Vincent's Hospital, Sydney, Sydney, Australia; [2]Neuroscience Research Australia (NeuRA), Sydney, Australia

442 Similar Neurocognitive Performance in Patients on ATV/r Monotherapy vs Triple Therapy

Giada Caramatti[1]; Francesca Ferretti[1]; Antonio Di Biagio[2]; Amedeo Capetti[3]; Andrea Antinori[4]; Fiorella Di Sora[5]; Roberta Gagliardini[6]; Concetta Vinci[1]; Adriano Lazzarin[1]; **Laura Galli**[1]

[1]San Raffaele Scientific Institute, Milan, Italy; [2]Azienda Ospedaliera San Martino, Genoa, Italy; [3]L. Sacco University Hospital, Milan, Italy; [4]National Institute for Infectious Diseases IRCCS Lazzaro Spallanzani, Rome, Italy; [5]Ospedale San Giovanni, Rome, Italy; [6]Catholic University of the Sacred Heart, Rome, Italy

443 Cerebrospinal Fluid Markers in Long-Term Atazanavir/Ritonavir Monotherapy

Francesca Ferretti; Alba Bigoloni; Valeria Longo; Laura Galli; Laura Passeri; Simonetta Gerevini; Vincenzo Spagnuolo; Adriano Lazzarin; Paola Cinque; Antonella Castagna

San Raffaele Scientific Institute, Milan, Italy

444 Neurocognitive Decline Is Associated With Antiretroviral Concentrations in Plasma and Cerebrospinal Fluid (CSF)

Qing Ma[1]; Xia Liu[2]; Robert Heaton[1]; Fujie Zhang[2]; Hua Jin[1]; Hao Wu[2]; Melanie Crescini[1]; Hongxin Zhao[2]; Hui Zeng[2]; Scott Letendre[1]

[1]University of California San Diego, San Diego, CA, US; [2]Chinese Center for Disease Control and Prevention, Beijing, China

445 Viral Decay Rate in the Cerebrospinal Fluid After Initiating Antiretroviral Therapy

Natalie M. Bowman[1]; Sarah B. Joseph; Prema Menezes[1]; Jessica Margolis[1]; Christopher Lippincott[1]; Michael J. Vinikoor[1]; Kevin R. Robertson[1]; Richard Price[2]; Ronald Swanstrom[1]; Joseph Eron[1]

[1]University of North Carolina, Chapel Hill, NC, US; [2]University of California San Francisco (UCSF), San Francisco, CA, US

446 Rates of Nonconfounded HIV-Associated Neurocognitive Disorder After Early cART

Teresa H. Evering[1]; Allison Applebaum[2]; Melissa La Mar[1]; Donald Garmon[1]; David Dorfman[3]; Martin Markowitz[1]

[1]Aaron Diamond AIDS Research Center, an Affiliate of the Rockefeller University, New York, NY, US; [2]Memorial Sloan-Kettering Cancer Center, New York, NY, US; [3]Mount Sinai School of Medicine, New York, NY, US

447 The Impact of HAART CNS Penetration Effectiveness on Brain Integrity in HIV+ Adults

Laurie Baker[1]; Robert H. Paul[1]; Jodi M. Heaps[1]; Mario Ortega[2]; Christin Usher[1]; Jee Yoon Chang[2]; Beau Ances[2]

[1]University of Missouri St Louis, St Louis, MO, US; [2]Washington University School of Medicine, St Louis, MO, US

448 Efavirenz Use is Not Associated with Increased Risk of Neuropsychological Impairment

Sean B. Rourke[1]; John Gill[2]; Anita Rachlis[1]; Colin Kovacs[4]; Gordon Arbess[5]; Jason Brunetta[4]; Adriana Carvalhal[1]; Chris Power[2]; Ann N. Burchell[3]; Tsegaye Bekele[3]

[1]University of Toronto, Toronto, Canada; [2]University of Alberta, Calgary, Canada; [3]The Ontario HIV Treatment Network, Toronto, Canada; [4]Maple Leaf Medical Clinic, Toronto, Canada; [5]St. Michael's Hospital, Toronto, Canada

449 Quantitative Electroencephalogram as a Translational Biomarker for NNRTI CNS AEs

Pamela Tannenbaum; Jacquelyn Binns; Spencer Tye; Alan Savitz; Steven Fox; Christopher Burgey; Ming-tain Lai; Arthur Simen; daria hazuda; **Michael D. Miller**

Merck and Co, Inc, West Point, PA, US

450 Neurocognition Following Antiretroviral Initiation in Behaviorally HIV-Infected Youth

Sharon Nichols[1]; Patricia Garvie[2]; Tiandong Li[3]; Weijia Ren[3]; Bill Kapogiannis[4]; Bret Rudy[5]; John Sleasman[6]; Steven Woods[7]; Ana Puga[2]

The Adolescent Medicine Trials Network for HIV/AIDS Interventions

[1]University of California San Diego, La Jolla, CA, US; [2]Children's Diagnostic & Treament Center, Inc., Ft. Lauderdale, FL, US; [3]Westat, Inc., Rockville, MD, US; [4]National Institutes of Health (NIH), Bethesda, MD, US; [5]New York University, New York, NY, US; [6]Duke University, Durham, NC, US; [7]University of California, San Diego, La Jolla, CA, US

WEDNESDAY, FEBRUARY 25, 2015

Session P-G3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Neurologic Disorders in Resource-Limited Settings

451 Neurocognitive Impairment in Diverse Resource-Limited Settings: The International Neurological Study ACTG A5199 and A5271

Kevin R. Robertson[1]; Hongyu Jiang[2]; Scott Evans[2]; Christina Marra[4]; Baiba Berzins[3]; James Hakim[5]; Ned Sacktor[6]; Thomas Campbell[7]; Ann Walawander[8]; Jeff Schouten[4]

On behalf of ACTG 5199 and 5271

[1]University of North Carolina Chapel Hill, Chapel Hill, NC, US; [2]Harvard University, Boston, MA, US; [3]Northwestern University, Chicago, IL, US; [4]University of Washington, Seattle, WA, US; [5]University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe; [6]Johns Hopkins University, Baltimore, MD, US; [7]University of Colorado, Denver, CO, US; [8]Frontier Science, Amherst, NY, US; [9]University of Washington, Seattle, WA, US

452 High Frequency of Dementia in Antiretroviral-Naïve HIV+ Individuals in Rural Uganda

Ned Sacktor[1]; Deanna R. Saylor[1]; Gertrude Nakigozi[2]; Noeline Nakasujja[3]; Xiangrong Kong[4]; Kevin Robertson[5]; Ronald H. Gray[4]; Maria J. Wawer[4]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Rakai Health Sciences Program, Entebbe, Uganda; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]University of North Carolina, Chapel Hill, NC, US

453 Validation of the International HIV Dementia Scale Screening Tool for HAND in Uganda

Megan M. Hosein[1]; Deanna Saylor[1]; Gertrude Nakigozi[2]; Noeline Nakasujja[3]; Xiangrong Kong[4]; Kevin Robertson[5]; Ronald H. Gray[4]; Maria J. Wawer[4]; Ned Sacktor[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Rakai Health Sciences Program, Kalisizo, Uganda; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]University of North Carolina Chapel Hill, Chapel Hill, NC, US

454 Cerebrospinal Fluid Cytokines and HIV-Associated Neurocognitive Disorders in Uganda

Mahsa Abassi[1]; Gertrude Nakigozi[3]; Noeline Nakasujja[2]; Xiangrong Kong[4]; David B. Meya[2]; Kevin Robertson[5]; Ronald H. Gray[4]; Maria J. Wawer[5]; Ned Sacktor[5]; David R. Boulware[1]

[1]University of Minnesota, Minneapolis, MN, US; [2]Infectious Disease Institute, Kampala, Uganda; [3]Rakai Health Sciences Program, Entebbe, Uganda; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]Johns Hopkins University School of Medicine, Baltimore, MD, US

455 A Comparison of 5 Brief Screening Tools for HAND in the USA and South Africa

John A. Joska[1]; Jade Witten[1]; Kevin Thomas[1]; Corne Robertson[1]; Martine Casson-Crook[1]; Heidi Roosa[2]; Jason Creighton[2]; Jennifer Lyons[3]; Justin McArthur[2]; **Ned Sacktor**[2]

[1]University of Cape Town, Cape Town, South Africa; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US

456 Subtype Associations With HIV-Associated Neurocognitive Dysfunction

Tyler R. Day; Davey M. Smith; Robert Heaton; Donald Franklin; Myres W. Tilghman; Josué Pérez-Santiago

University of California San Diego, San Diego, CA, US

457 Peripheral Neuropathy at First-Line Failure and on Second Line in Sub-Saharan Africa

Alejandro Arenas-Pinto[1]; Jennifer Thompson[1]; Godfrey Musoro[4]; Helen Mussana[5]; Abbas Lugemwa[3]; Andrew D. Kambugu[2]; Aggrey Mweemba[6]; Sarah Walker[1]; Paton Nicholas[1]
On behalf of the EARNEST Trial Team

[1]University College London, London, United Kingdom; [2]Makerere University, Kampala, Uganda; [3]Joint Clinical Research Centre, Mbarara, Uganda; [4]University of Zimbabwe, Harare, Zimbabwe; [5]Joint Clinical Research Centre, Kampala, Uganda; [6]University Teaching Hospital, Lusaka, Zambia

458 Prevalence of and Risk Factors for Peripheral Neuropathy in Rakai, Uganda

Deanna R. Saylor[1]; Gertrude Nakigozi[2]; Noeline Nakasujja[3]; Xiangrong Kong[4]; Kevin Robertson[5]; Ronald H. Gray[4]; Maria J. Wawer[4]; Ned Sacktor[1]

[1]Johns Hopkins School of Medicine, Baltimore, MD, US; [2]Rakai Health Sciences Program, Entebbe, Uganda; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]University of North Carolina, Chapel Hill, NC, US

459 Predictors of Cognitive Performance Among HIV-Infected Patients in East Africa

Victor G. Valcour[1]; Francis Kiweewa[2]; Rosemary Namagembe[2]; Rither Langat[3]; Samoel Khamadi[4]; Kyra Hansson[1]; Christina S. Polyak[5]; Julie Ake[5]
On behalf of the RV329 AFRICOS Study Team

[1]University of California San Francisco, San Francisco, CA, US; [2]Walter Reed Project, Kampala, Uganda; [3]Walter Reed Project, Kericho, Kenya; [4]Walter Reed Project - Tanzania, Mbeya, United Republic of Tanzania; [5]Walter Reed Army Institute of Research, Silver Spring, MD, US

THURSDAY, FEBRUARY 26, 2015

Session P-G4 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HAND Genetics

460 Mitochondrial DNA Haplogroups and CSF Neuroinflammation in the CHARTER Cohort

Todd Hulgan[4]; David Samuels[4]; Ronald J. Ellis[1]; William Bush[2]; Scott Letendre[1]; Donald Franklin[1]; Igor Grant[1]; Asha R. Kallianpur[3]
CHARTER Group

[1]University of California San Diego, San Diego, CA, US; [2]Case Western Reserve University, Cleveland, OH, US; [3]Cleveland Clinic Foundation, Lerner Research Institute, Cleveland, OH, US; [4]Vanderbilt University, Nashville, TN, US

461 Iron-Regulatory Genes Are Associated With Neuroimaging Traits in HIV Infection

Tricia A. Thornton-Wells[2]; Christine Fennema-Notestine[3]; Todd Hulgan[4]; Scott Letendre[5]; Ronald J. Ellis[6]; **Asha R. Kallianpur**[1]; for the CHARTER Group[7]

[1]Cleveland Clinic/Lerner Research Institute, Cleveland, OH, US; [2]Vanderbilt University School of Medicine, Nashville, TN, US; [3]University of California San Diego, San Diego, CA, US; [4]Vanderbilt University School of Medicine, Nashville, TN, US; [5]University of California San Diego, San Diego, CA, US; [6]University of California San Diego, San Diego, CA, US; [7]University of California San Diego (UCSD), San Diego, CA, US

462 Synergistic Effects of *MBL2*/*APP* Polymorphisms on Neurocognitive Impairment in CHARTER

Kumud Singh; Qianqian Deng; Christine Fennema-Notestine; Florin Vaida; Ronald Ellis; Scott Letendre; Donald Franklin; Debralee Rosario; Robert Heaton; Igor Grant
CHARTER

University of California San Diego, La Jolla, CA, US

463 No Association Between Apoε4, HIV Infection, Age, Cognitive Outcome or Death

James T. Becker[1]; Jeremy J. Martinson[1]; Sudhir Penugonda[2]; Lawrence Kingsley[1]; Samantha A. Molsberry[1]; Sandra Reynolds[3]; Andrew Levine[4]; Eileen Martin[5]; Cynthia A. Munro[6]; Ned Sacktor[6]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [4]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US; [5]Rush University Medical Center, Chicago, IL, US; [6]Johns Hopkins University School of Medicine, Baltimore, MD, US

464 Bridging Genetics, Histopathology, and Neurocognition in the Context of HAND

Andrew Levine[1]; Virawudh Soontornniyomkij[2]; Cristian L. Achim[2]; Ben Gouaux[2]; Eliezer Masliah[2]; Janet Sinsheimer[3]; Elyse Singer[1]; David J. Moore[2]

[1]University of California Los Angeles, Long Beach, CA, US; [2]University of California San Diego, San Diego, CA, US; [3]University of California Los Angeles, Los Angeles, CA, US

TUESDAY, FEBRUARY 24, 2015

Session P-G5 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HAND Diagnosis and Predictors

465 Relative Risk and Factors Associated With Progression to Symptomatic HAND

Sean B. Rourke[1]; John Gill[2]; Anita Rachlis[1]; Colin Kovacs[3]; Gordon Arbess[5]; Jason Brunetta[3]; Adriana Carvalhal[5]; Chris Power[2]; Ann N. Burchell[4]; Tsegaye Bekele[4]

[1]University of Toronto, Toronto, Canada; [2]University of Alberta, Calgary, Canada; [3]Maple Leaf Medical Clinic, Toronto, Canada; [4]The Ontario HIV Treatment Network, Toronto, Canada; [5]St. Michael's Hospital, Toronto, Canada

466 Monocytes Activation Characterizes Immune Failure but Not Cognitive Impairment on ART

Antonio Muscatello[1]; Davide Mangioni[1]; Paolo Perseghin[2]; Arianna Incontri[2]; Alessandro Soria[1]; Nicola Squillace[1]; Giuseppe Lapadula[1]; Sebastiano Leone[1]; Andrea Gori[1]; **Alessandra Bandera**[1]

[1]S. Gerardo Hospital, Monza, Italy; [2]San Gerardo Hospital–UOS Aferesi e Nuove Tecnologie Trasfusionali–SIMT, Monza, Italy

467 The VACS Index Predicts Change in Neurocognitive Functions in People With HIV

Sean B. Rourke[1]; John Gill[2]; Anita Rachlis[1]; Amy Justice[7]; Colin Kovacs[3]; Gordon Arbess[4]; Jason Brunetta[3]; Adriana Carvalhal[4]; Chris Power[6]; Ann N. Burchell[5]

[1]University of Toronto, Toronto, Canada; [2]University of Alberta, Calgary, Canada; [3]Maple Leaf Medical Clinic, Toronto, Canada; [4]St. Michael's Hospital, Toronto, Canada; [5]The Ontario HIV Treatment Network, Toronto, Canada; [6]University of Alberta, Edmonton, Canada; [7]Yale University School of Medicine, New Haven, CT, US

468 When Diagnosing HAND, Should Visuospatial Functioning be Evaluated?

Talia Shirazi[1]; Angela Summers[1]; Sally Steinbach[2]; Suad Kapetanovick[1]; Avindra Nath[2]; Bryan Smith[2]; Joseph Snow[1]

[1]National Institute of Mental Health (NIMH), Bethesda, MD, US; [2]National Institute of Neurological Disorders and Stroke, Bethesda, MD, US

469 Predictors of Neurocognitive Decline Among Aviremic Individuals in the CHARTER Cohort

Marie-Josée Brouillette[1]; Tracy Yuen[2]; Susan C. Scott[2]; Lesley K. Fellows[3]; Robert Heaton[4]; Scott Letendre[4]; Ronald J. Ellis[4]; Nancy Mayo[2]
the CHARTER group

[1]McGill University Health Centre, Montreal, Canada; [2]McGill University Health Centre, Montreal, Canada; [3]Montreal Neurological Hospital, Montreal, Canada; [4]University of California San Diego, San Diego, CA, US

470 Association Between Plasma Homocysteine Levels and Neuronal Injury in Untreated HIV

Erika Ahlgren[1]; Lars Hagberg[1]; Lars-Magnus Andersson[1]; Staffan Nilsson[2]; Dietmar Fuchs[3]; Henrik Zetterberg[1]; Magnus Gisslén[1]

[1]University of Gothenburg, Gothenburg, Sweden; [2]Chalmers University of Technology, Gothenburg, Sweden; [3]Innsbruck Medical University, Innsbruck, Austria

471 Plasma MicroRNA Profiling Predicts HIV-Associated Neurocognitive Disorder

Eugene L. Asahchop[1]; William G. Branton[1]; Segun M. Akinwumi[2]; Noshin Koenig[3]; Esther Fujiwara[2]; John Gill[3]; Christopher Power[1]

[1]University of Alberta, Edmoton, Canada; [2]University of Alberta, Edmonton, Canada; [3]Southern Alberta Clinic, Calgary, Canada

472 Performance of 4 Tools to Screen for HIV-Associated Cognitive Impairment

Judith Schouten[2]; Tanja Su[2]; **Rosan A. van Zoest**[1]; Ferdinand W. Wit[1]; Ineke G. Stolte[5]; Alan Winston[3]; Peter Reiss[1]; Peter Portegies[4]; Gert J. Geurtsen[2]; Ben A. Schmand[2]

[1]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands; [2]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [3]Imperial College London, London, Netherlands; [4]Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands; [5]Public Health Service of Amsterdam, Amsterdam, Netherlands

THURSDAY, FEBRUARY 26, 2015

Session P-G6 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Inflammation and Markers of Brain Injury in HAND

473 Astrocyte and Microglial Activation in Acute and Chronic HIV Pre- and Post-cART

Michael Peluso[1]; Victor G. Valcour[2]; Jintanat Ananworanich[3]; James L. Fletcher[4]; Somporn Tipsuk[4]; Bonnie Slike[3]; Nittaya Phanuphak[4]; Magnus Gisslén[5]; Henrik Zetterberg[5]; **Serena Spudich**[6]

RV254/SEARCH 010 & SEARCH 011 Study Teams

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [2]University of California San Francisco, San Francisco, CA, US; [3]Walter Reed Army Institute of Research, Bethesda, MD, US; [4]Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [5]University of Gothenburg, Gothenburg, Sweden; [6]Yale University, New Haven, CT, US

474 CNS Immunoactivation and Neuronal Damage in Patients With Progressive Neurocognitive Impairment

Arvid Edén[1]; Donald Franklin[2]; Henrik Zetterberg[1]; Dietmar Fuchs[3]; Robert Heaton[2]; Scott Letendre[2]; Thomas Marcotte[2]; Richard Price[4]; Igor Grant[2]; Magnus Gisslén[1]

[1]University of Gothenburg, Gothenburg, Sweden; [2]University of California San Diego, San Diego, CA, US; [3]Innsbruck Medical University, Innsbruck, Austria; [4]University of California San Francisco, San Francisco, CA, US

475 Endothelial Function and CNS Measures in Primary HIV Infection Pre and Post Early ART

Sebastian Urday[1]; **Zaina Zayyad**[1]; Julia Peterson[2]; Felicia C. Chow[2]; Kevin R. Robertson[3]; Richard Price[2]; Priscilla Hsue[2]; Serena Spudich[1]

[1]Yale University, New Haven, CT, US; [2]University of California San Francisco, San Francisco, CA, US; [3]University of North Carolina, Chapel Hill, NC, US

476 Platelet-Endothelial Interactions in SIV-Associated CNS Disease

Claire E. Lyons[2]; Hannah Schneider[3]; Liz Engle[1]; Suzanne E. Queen[1]; Craig N. Morrell[4]; Joseph L. Mankowski[1]; **Kelly A. Pate**[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Tufts University, North Grafton, MA, US; [3]Colorado State University, Fort Collins, CO, US; [4]University of Rochester, Rochester, NY, US

477 Microbial Translocation Is Associated With Neuroinflammation in HIV Subjects on ART

Jaime H. Vera[1]; Qi Guo[2]; Adriano Boasso[1]; Louise Greathead[1]; James Cole[1]; Courtney Bishop[2]; Rabiner Ilan[2]; Roger Gunn[2]; Paul Matthews[1]; Alan Winston[1]

[1]Imperial College London, London, United Kingdom; [2]Imanova Centre for Imaging Sciences, London, United Kingdom

478 DKK1 Is Associated With HIV-Associated Neurocognitive Impairment

Chunjiang Yu[1]; Melanie Seaton[1]; Scott Letendre[2]; Robert Heaton[2]; **Lena Al-Harthi**[1]

[1]Rush University Medical Center, Chicago, IL, US; [2]University of California at San Diego, San Diego, CA, US

479 Markers of HIV-Associated Cognitive Impairment Are Elevated in HIV-Infected Patients With Neurosyphilis

Emily Ho; Lauren Tantalo; Sharon Sahi; Trudy Jones; Shelia Dunaway; Christina Marra

University of Washington, Seattle, WA, US

480 CD14+ PBMC Secrete Cytokines Linked to HIV-Associated Neurocognitive Disorders

Melissa A. Agsalda-Garcia[4]; Victor G. Valcour[1]; Pasiri Sithinamsuwan[2]; Guangxiang G. Zhang[4]; Cecilia M. Shikuma[4]; James L. Fletcher[3]; Nicholas Hutchings[1]; Alexandra Schuetz[5]; Jintanat Ananworanich[3]; Bruce Shiramizu[4]

[1]University of California San Francisco, San Francisco, CA, US; [2]Phramongkutklao Hospital, Bangkok, Thailand; [3]The Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [4]University of Hawaii, John A. Burns School of Medicine, Honolulu, HI, US; [5]Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand

481 MBL-HIV1gp120 Immunoreactivity Is Associated With Markers of Neuronal Injury

Carmen Teodorof[1]; Damhnien Nguyen[1]; Nishi Kadakia[1]; Ricky Maung[2]; Benchawanna Soontornniyomkij[1]; Cristian Achim[1]; David Moore[1]; Eliezer Masliah[1]; Marcus Kaul[2]; Kumud Singh[1]

[1]University of California San Diego, San Diego, CA, US; [2]The Sanford Burnham Medical Research Institute, La Jolla, CA, US

WEDNESDAY, FEBRUARY 25, 2015

Session P-G7 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Aging and Cognitive Decline

482 Amyloid Uptake by PET Imaging in Older HIV+ Individuals With Cognitive Impairment

Ned Sacktor; Richard Skolasky; Heidi Roosa; Yun Zhou; Weiguo Ye; Noble George; Dean Wong; Mona Mohamed

Johns Hopkins University School of Medicine, Baltimore, MD, US

483 Lower CSF Amyloid-β Levels Are Associated With Worse Neurocognitive Functioning in HIV-Infected Adults With a Family History of Dementia

Pariya L. Fazeli[1]; David J. Moore[1]; Donald Franklin[1]; Robert Heaton[1]; Christina Marra[2]; Benjamin B. Gelman[3]; Allen McCutchan[1]; Igor Grant[1]; Scott Letendre[1]

[1]University of California San Diego, San Diego, CA, US; [2]University of Washington Seattle, Seattle, WA, US; [3]University of Texas Medical Branch, Galveston, TX, US

484 Cystatin C Is Associated With Neurocognitive Impairment in Older HIV+ Adults

Marissa Sakoda[1]; Pariya L. Fazeli[2]; Scott Letendre[2]; Dilip Jeste[2]; Igor Grant[2]; David J. Moore[2]

[1]John A. Burns School of Medicine at the University of Hawaii, Honolulu, HI, US; [2]University of California San Diego, San Diego, CA, US

485 Leptomeningeal Enhancement on MRI in the Aging HIV-Positive Population

Bryan R. Smith[1]; Sally Steinbach[1]; Govind Nair[1]; Caryn Morse[1]; Joseph Snow[2]; Suad Kapetanovick[2]; Henry Masur[1]; Avindra Nath[1]; Daniel S. Reich[1]

[1]National Institutes of Health, Bethesda, MD, US; [2]National Institute of Mental Health, Bethesda, MD, US; [3]National Institutes of Health, Clinical Center, Bethesda, MD, US

486 Hepatitis C Infection and Cognition in Older HIV+ Adults: Data From the Center of Excellence on Disparities in HIV and Aging (CEDHA)

Oluwatoyin M. Adeyemi[1]; Sue Leurgans[2]; Alan Landay[2]; David Bennett[2]; Lisa Barnes[2]

[1]Ruth M Rothstein CORE Center, Cook County Health and Hospitals System, Chicago, IL, US; [2]Rush University Medical Center, Chicago, IL, US

487 Neurocognitive Screening Tests Are Associated With Cardiovascular Risk and VACS Scores

Andrea Calcagno[1]; Marielisabetta Scarvaglieri[1]; Daniela Vai[2]; Alessandro Livelli[2]; Letizia Marinaro[1]; Giancarlo Orofino[2]; Nicole Pagani[1]; Daniele Imperiale[2]; Giovanni Di Perri[1]; Stefano Bonora[1]

[1]University of Torino, Torino, Italy; [2]ASLTO2, Torino, Italy; [3]ASLTO2, Torino, Italy

488 Aerobic Exercise Attenuates Cognitive Decline and Brain Volume Loss Associated With HIV

Brian Basco[1]; Mario Ortega[1]; Jodi M. Heaps[3]; Laurie Baker[2]; Florin Vaida[4]; Beau Ances[1]

[1]Washington University School of Medicine, St. Louis, MO, US; [2]University of Missouri St. Louis, St. Louis, MO, US; [3]Missouri Institute of Mental Health, St. Louis, MO, US; [4]University of California San Diego, San Diego, CA, US

489 The Impact of Physical Activity on Cognition in Men With and Without HIV

Anne Monroe[1]; Long Zhang[7]; Lisa P. Jacobson[7]; Todd T. Brown[1]; Michael Plankey[4]; Eric Miller[3]; James T. Becker[5]; Eileen Martin[6]; Ned Sacktor[1]
On behalf of the Multicenter AIDS Cohort Study

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]University of California Los Angeles, Los Angeles, CA, US; [4]Georgetown University, Washington, DC, US; [5]University of Pittsburgh, Pittsburgh, PA, US; [6]Rush University Medical Center, Chicago, IL, US; [7]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

490 Abnormal Lung Function Associated With Abnormal Brain Structure and Function in HIV

Alison Morris[1]; Lawrence Kingsley[1]; **Matthew Gingo**[1]; Meghan Fitzpatrick[1]; Roger Detels[3]; Oto Martinez[3]; Eric Miller[3]; Jeffrey Alger[3]; Eric Kleerup[3]; James T. Becker[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]University of Pittsburgh, Pittsburgh, PA, US; [3]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US

491 HIV DNA and Neurocognitive Impairment in Older Subjects on Suppressive ART

Michelli Faria de Oliveira[1]; Ben Murrell[1]; Josué Pérez-Santiago[1]; Milenka Vargas[1]; Ronald J. Ellis[2]; Scott Letendre[2]; Igor Grant[2]; Davey M. Smith[1]; Steven P. Woods[2]; Sara Gianella[1]

[1]University of California San Diego, La Jolla, CA, US; [2]HIV Neurobehavioral Research Center, San Diego, CA, US

492 Suppressive ART Is Key to Reduce Neurocognitive Impairment in Aging HIV+ Individuals

Christina C. Yek[1]; David M. Smith[1]; Gabriel Wagner[1]; Susan Morgello[2]; Scott Letendre[1]; Igor Grant[1]; Sergei L. Kosakovsky Pond[1]; Sara Gianella[1]
On behalf of the CHARTER group

[1]University of California San Diego, San Diego, CA, US; [2]Icahn School of Medicine at Mount Sinai, New York, NY, US

493 Mixed Membership Trajectory Model of Cognitive Impairment in the MACS

Samantha A. Molsberry[1]; Fabrizio Lecci[2]; Brian Junker[2]; Sandra Reynolds[3]; Andrew Levine[4]; Eileen Martin[5]; Cynthia A. Munro[6]; Ned Sacktor[6]; James T. Becker[1]; Neuropsychology Working Group O. Multicenter AIDS Cohort Study[7]

[1]University of Pittsburgh, Boston, MA, US; [2]Carnegie Mellon University, Pittsburgh, PA, US; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [4]University of California Los Angeles, Los Angeles, CA, US; [5]Rush University Medical Center, Chicago, IL, US; [6]Johns Hopkins University School of Medicine, Baltimore, MD, US; [7]National Institutes of Health (NIH), Bethesda, MD, US

494 Brain Structural Correlates of Trajectories to Cognitive Impairment in HIV Disease

James T. Becker[1]; Mikhail Popov[1]; Samantha A. Molsberry[1]; Fabrizio Lecci[2]; Brian Junker[2]; Sandra Reynolds[3]; Eric Miller[4]; Cynthia A. Munro[5]; Ann Ragin[6]; Ned Sacktor[5]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]Carnegie Mellon University, Pittsburgh, PA, US; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [4]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US; [5]Johns Hopkins University School of Medicine, Baltimore, MD, US; [6]Northwestern University, Feinberg School of Medicine, Chicago, IL, US

495 Cognitive Reserve and Neuropsychological Functioning in Older HIV-Infected People

Benedetta Milanini[1]; Nicoletta Ciccarelli[1]; Silio Limiti[1]; Pierfrancesco Grima[2]; Massimiliano Fabbiani[1]; Barbara Rossetti[3]; Elena Visconti[1]; Enrica Tamburrini[1]; Roberto Cauda[1]; Simona Di Giambenedetto[1]

[1]Institute of Infectious Diseases, Catholic University of Sacred Hearth, Rome, Italy; [2]Division of Infectious Diseases, "S. Caterina Novella" Hospital, Galatina, Italy; [3]Division of Infectious Diseases, University of Siena, Italy

THURSDAY, FEBRUARY 26, 2015

Session P-G8 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Mitochondrial Dysfunction in HAND and Depression

496 Mitochondrial DNA, Neurologic and Systemic Inflammation, and Immune Dysregulation

Josué Pérez-Santiago; Michelli Faria de Oliveira; Susanna R. Var; Steven P. Woods; Sara Gianella Weibel; Sanjay Mehta; Ben Murrell; Tyler R. Day; Ronald J. Ellis

University of California San Diego, La Jolla, CA, US

497 CSF Metabolomics Implicate Bioenergetic Adaptation as a Neural Mechanism Regulating Shifts in the Cognitive States of HIV-Infected Subjects

Norman J. Haughey[1]; Alex DIckens[1]; Reena Deutsch[2]; Michelle Mielke[3]; Timothy Claridge[4]; Igor Grant[2]; Thomas Marcotte[2]; Scott Letendre[2]; Justin McArthur[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]University of California San Diego, San Diego, CA, US; [3]Mayo Clinic, Rochester, MN, US; [4]University of Oxford, Oxford, United Kingdom

498 Altered Monoamine and Acylcarnitine Metabolites in HIV Patients with Depression

Edana Cassol[1]; Vikas Misra[2]; Susan Morgello[3]; Gregory D. Kirk[4]; Shruti H. Mehta[4]; Dana H. Gabuzda[2]

[1]Carleton University, Ottawa, Canada; [2]Dana-Farber Cancer Institute, Boston, MA, US; [3]Mount Sinai Hospital, New York, NY, US; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

499 Mitochondrial Injury and Cognitive Function in HIV Infection and Methamphetamine

Susanna R. Var; Tyler R. Day; Andrej Vitomirov; Davey M. Smith; Virawudh Soontornniyomkij; Cristian L. Achim; Sanjay Mehta; Josué Pérez-Santiago

University of California San Diego, San Diego, CA, US

500 Efavirenz-Induced Nitric Oxide Affects Mitochondrial Function in Glial Cells

Haryes A. Funes[1]; Fernando Alegre[2]; Miriam Polo[2]; Ana Blas-García[2]; **Juan V. Espluges**[3]; Nadezda Apostolova[4]

[1]Universidad de Valencia, Valencia, Spain; [2]Universidad de Valencia/FISABIO, Valencia, Spain; [3]Universidad de Valencia/FISABIO/CIBERehd, Valencia, Spain; [4]Universidad Jaume I, Castellón, Spain

Session P-G9 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Neuropathogenesis Mechanisms

501 Role of HIV Strain, Accessory Proteins, and Cytokines in Macrophage HO-1 Deficiency

Alexander J. Gill; Patricia J. Vance; Ronald G. Collman; Dennis L. Kolson

University of Pennsylvania, Philadelphia, PA, US

502 Atorvastatin Reverses the HIV-induced HO-1 Defect in Primary Human Macrophages

Melanie R. Duncan; Alexander J. Gill; Anjana Yadav; Dennis L. Kolson; Ronald G. Collman

University of Pennsylvania, Philadelphia, PA, US

503 Enhanced Antagonism of BST-2 by Neurovirulent SIV Envelope

Kenta Matsuda; Chia-Yen Chen; Fan Wu; Ronald Plishka; Alicia Buckler-White; Klaus Strebel; Vanessa M. Hirsch

National Institutes of Health (NIH), Bethesda, MD, US

504 MEMRI Reflects HIV-1-Associated Human Pathobiology in a Rodent NeuroAIDS Model

Aditya N. Bade; Santhi Gorantla; Prasanta K. Dash; Edward Makarov; Balasrinivasa R. Sajja; Larisa Poluektova; Howard Gendelman; Michael Boska; Yutong Liu

University of Nebraska Medical Center, Omaha, NE, US

505 Detectable CSF Tat Despite Dual Compartment HIV Viral Suppression With cART

Bruce Brew[1]; Lucette A. Cysique[2]; Simon Jones[4]; Tory Johnson[3]; Avindra Nath[3]

[1]St Vincent's Hospital, Sydney, Sydney, Australia; [2]Neuroscience Research Australia, Sydney, Australia; [3]National Institute of Neurological Disorders and Stroke, Bethesda, MD, US; [4]St Vincent's Centre for Applied Medical Research, Sydney, Australia

506 DNA Methylation Changes in HIV-Positive Men With Cognitive Decline

Jeremy Martinson; Gregory Joseph; Lawrence Kingsley; James T. Becker
Pitt Mens Study

University of Pittsburgh, Pittsburgh, PA, US

507 HIV Induces Astrocyte Senescence and Is Reversed by Beta-Catenin Induction

Chunjiang Yu; **Victoria Lutgen**; Lena Al-Harthi

Rush University Medical Center, Chicago, IL, US

508 Wnts-Mediated Astrocyte/CD8+ T-Cell Interactions Impacting HIV Neuropathogenesis

Maureen H. Richards[1]; Melanie S. Seaton[1]; Stephanie Kim[2]; Srinivasa Narasipura[1]; Lena Al-Harthi[1]

[1]Rush University Medical Center, Chicago, IL, US; [2]Brown University, Boston, MA, US

TUESDAY, FEBRUARY 24, 2015

Session P-H1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Pharmacokinetics, Pharmacodynamics, and Adherence

509 HIV-1 Attachment Inhibitor Prodrug BMS-663068: Model-Based Dose Selection

Ishani Savant Landry[1]; Li Zhu[1]; Malaz Abutarif[1]; Matthew Hruska[1]; Brian M. Sadler[2]; Maria Pitsiu[3]; George J. Hanna[1]; David W. Boulton[1]; Richard Bertz[1]

[1]Bristol-Myers Squibb, Princeton, NJ, US; [2]ICON plc, Cary, NC, US; [3]ICON plc, Manchester, United Kingdom

510 Pharmacokinetic and Pharmacodynamic Evaluation of NNRTI IQP-0528 DuoGel™ in Macaques

Lara E. Pereira[1]; Pedro Mesquita[2]; **Anthony Ham**[3]; Tyana Singletary[4]; Janet McNicholl[5]; Karen W. Buckheit[3]; Robert Buckheit[3]; James M. Smith[5]

[1]LifeSource Biomedical LLC,, Moffett Field, CA, US; [2]Albert Einstein College of Medicine, Bronx, NY, US; [3]ImQuest BioSciences,, Frederick, MD, US; [4]Anyar Inc., Fort Walton Beach, FL, US; [5]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

511 Tenofovir PK in Adults With Renal Dysfunction on LPV/r and NNRTI-Based ART

Tim R. Cressey[1]; Anchalee Avihingsanon[2]; Guttiga Halue[3]; Prattana Leenasirimakul[4]; Praornsuda Sukrakanchana[5]; Anthony T. Podany[6]; Courtney Fletcher[6]; Gonzague Jourdain[5]; Virat Klinbuayaem[7]; Chureeratana Bowonwatanuwong[8]

[1]PHPT-IRD UMI 174 Chiang Mai University/Harvard School of Public Health, Chiang Mai, Thailand; [2]HIV Netherlands Australia Thailand Research Collaboration, Bangkok, Thailand; [3]Phayao Hospital, Phayao, Thailand; [4]Nakornping Hospital, Chiang Mai, Thailand; [5]Chiang Mai University, Chiang Mai, Thailand; [6]University of Nebraska Medical Center, Omaha, NE, US; [7]Sanpatong Hospital, Sanpatong, Thailand; [8]Chonburi Hospital, Chonburi, Thailand

512 Population Pharmacokinetics of Cotrimoxazole West African HIV-Infected Children

Claire Pressiat[1]; Sihem Benaboud[2]; Jean-Marc Treluyer[1]; Véronique Méa-Assande[3]; Caroline Yonaba[4]; Sophie Dattez[5]; Diarra Ye[6]; Yi ZHENG[1]; **Valeriane Leroy**[5]; Déborah HIRT[1]
MONOD ANRS 12206

[1]Paris Descartes University, EA 08, Paris, France; [2]Clinical Pharmacology Department, AP-HP, Paris Centre Hospital Group, Paris, France; [3]Avocatier Health Center, Abidjan, Côte d'Ivoire; [4]Department of Paediatrics, CHU Yalgado Ouedraogo, Ouagadougou, Burkina Faso; [5]Institute of Public Health, Epidemiology and Development (ISPED), University of Bordeaux, Bordeaux, France; [6]Department of Paediatrics, CHU Charles de Gaulle, Université de Ouagadougou, Ouagadougou, Burkina Faso

513 ART Choice Impacts Antimalarial Exposure and Treatment Outcomes in Ugandan Children

Sunil Parikh[2]; Norah Mwebaza[3]; Richard Kajubi[3]; Joshua Ssebuliba[3]; Sylvia Kiconco[3]; Liusheng Huang[1]; Qin Gao[1]; Abel Kakuru[3]; Jane Achan[3]; **Francesca T. Aweeka**[1]

[1]University of California, San Francisco, San Francisco, CA, US; [2]Yale University, New Haven, CT, US; [3]Makerere University College of Health Sciences, Kampala, Uganda

514 Exploring Long-Term Adherence Markers Using Hair and Dried Blood Spots in iPrEX OLE

Monica Gandhi[1]; David V. Glidden[1]; Albert Liu[2]; Peter L. Anderson[7]; Howard Horng[1]; Juan Guanira[3]; Beatriz Grinsztejn[4]; Suwat Chariyalertsak[5]; Linda-Gail Bekker[6]; Robert M. Grant[1]
iPrEX OLE

[1]University of California San Francisco, San Francisco, CA, US; [2]San Francisco Department of Public Health, San Francisco, CA, US; [3]Investigaciones Medicas en Salud, Lima, Peru; [4]Instituto de Pesquisa Clinica Evandro Chagas, Rio de Janeiro, Brazil; [5]Chiang Mai University, Chiang Mai, Thailand; [6]University of Cape Town, Cape Town, South Africa; [7]University of Colorado, Denver, CO, US

Session P-H2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Pharmacogenomics

515 UGT1A1 Genotype Predicts Bilirubin-Related Discontinuation of Atazanavir/Ritonavir

Saran Vardhanabhuti[1]; Heather J. Ribaudo[1]; Raphael J. Landovitz[2]; Igho Ofotokun[3]; Jeffrey L. Lennox[3]; Judith S. Currier[2]; Lana M. Olson[4]; David W. Haas[4]

[1]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [2]UCLA Center for Clinical AIDS Research & Education, Los Angeles, CA, US; [3]Emory University School of Medicine, Atlanta, GA, US; [4]Vanderbilt University School of Medicine, Nashville, TN, US

516 ABCB1 Polymorphism Affects Tenofovir Exposure as Determined by Areas-Under-the-Time-Concentration-Curve With 24-hour Intensive Pharmacokinetic Monitoring

Sanjiv M. Baxi[1]; Peter Bacchetti[1]; Mardge Cohen[2]; Jack A. Dehovitz[3]; Kathryn Anastos[4]; Stephen J. Gange[5]; Mary A. Young[6]; Monica Gandhi[1]; Bradley Aouizerat[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]John Stroger (formerly Cook County) Hospital, Chicago, IL, US; [3]State University of New York Downstate Medical Center, Brooklyn, NY, US; [4]Montefiore Medical Center, University Hospital for Albert Einstein College of Medicine, Bronx, NY, US; [5]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [6]Georgetown University, Washington, DC, US

517 Pharmacogenomics of Plasma Tenofovir Clearance and Change in Creatinine Clearance

Valentine Wanga[1]; Charles Venuto[2]; Gene D. Morse[3]; Edward A. Acosta[5]; Eric Daar[4]; David W. Haas[1]; Chun Li[1]; Bryan E. Shepherd[1]

[1]Vanderbilt University School of Medicine, Nashville, TN, US; [2]University of Rochester Medical Center, Rochester, NY, US; [3]State University of New York at Buffalo, Buffalo, NY, US; [4]Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, US; [5]University of Alabama at Birmingham, Birmingham, AL, US

518 Variant ITPA Phenotypes Are Associated With Increased Ribavirin Triphosphate Levels

Leah C. Jimmerson[1]; Thomas J. Urban[2]; Eric Meissner[3]; Ariel Hodara[1]; Jacob A. Langness[4]; Christina Aquilante[1]; Aimee Truesdale[5]; Fafa Baouchi-Mokrane[5]; Michelle Ray[1]; Jennifer J. Kiser[1]

[1]University of Colorado, Aurora, CO, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]NIAID, NIH, Bethesda, MD, US; [4]University of Colorado Health, Aurora, CO, US; [5]Denver Health and Hospital Authority, Denver, CO, US

Session P-H3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Drug-Drug Interactions

519 Interactions of Antiretroviral Drugs With the SLC22A1 (OCT1) Drug Transporter

Darren M. Moss; Neill Liptrott; Marco Siccardi; Andrew Owen

University of Liverpool, Liverpool, United Kingdom

520 EFV but Not ATV/r Significantly Reduces Atovaquone Concentrations in HIV+ Subjects

Monica M. Calderon[4]; Joseph A. Kovacs[2]; Alice K. Pau[2]; Maryellen McManus[2]; Raul Alfaro[1]; Parag Kumar[1]; Scott R. Penzak[3]

[1]National Institutes of Health (NIH), Bethesda, MD, US; [2]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US; [3]University of North Texas System College of Pharmacy, Forth Worth, TX, US; [4]US Food and Drug Administration (FDA), Silver Spring, MD, US

521 The Effect of Single and Multiple Dose Rifampin on the Pharmacokinetics of Doravirine

Ka Lai Yee[3]; Sauzanne G. Khalilieh[2]; Rachael Liu[3]; Rosa Sanchez[3]; Matt S. Anderson[4]; Candice Smith-Bradley[5]; Joan Butterton[6]; Timothy Judge[1]; Helen Manthos[1]; John Brejda[1]

[1]Celerion, Lincoln, NE, US; [2]Merck and Co, Inc, Kenilworth, NJ, US; [3]Merck and Co., Inc., West Point, PA, US; [4]Merck and Co, Inc, Rahway, NJ, US; [5]Merck and Co, Inc, Upper Gwynedd, PA, US; [6]Merck and Co, Inc, Boston, MA, US

522 Drug-Drug Interaction Between HCV Inhibitors Grazoprevir/Elbasvir With Dolutegravir

Wendy W. Yeh[1]; Ted Marenco[2]; Hwa-Ping Feng[1]; Zifang Guo[1]; Daria Stypinski[2]; Lisa Ross[3]; Ivy H. Song[4]; Patricia Jumes[1]; Barbara Cook[2]; Joan R. Butterton[1]

[1]Merck & Co, Inc, Boston, MA, US; [2]Celerion, Lincoln, NE, US; [3]ViiV Healthcare, Research Triangle Park, NC, US; [4]GlaxoSmithKline, Research Triangle Park, NC, US

523 HIV-1 Attachment Inhibitor Prodrug BMS-663068: Interactions with DRV/r and/or ETR

Ishani Savant Landry; Xiaolu Tao; Jeffrey Anderson; Michael Hesney; Michele Stonier; Susan Lubin; Jian Wang; George J. Hanna; David W. Boulton

Bristol-Myers Squibb, Princeton, NJ, US

THURSDAY, FEBRUARY 26, 2015

Session P-H4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Pharmacokinetics in Compartments and Reservoirs and of Novel Formulations

524 Local and Systemic Pharmacokinetic Profile of Dapivirine Vaginal Ring-004 When Used Continuously Over Various Periods up to Twelve Weeks

Annalene M. Nel[1]; Wouter Haazen[2]; Marisa Russell[1]; Jeremy P. Nuttall[3]; Neliette Van Niekerk[1]; Nicoline Treijtel[4]

[1]International Partnership for Microbicides, Paarl, South Africa; [2]SGS Life Science Services, Antwerp, Belgium; [3]International Partnership for Microbicides, Silver Spring, MD, US; [4]Kinesis Pharma BV, Breda, Netherlands

525 Steady-state TDF/FTC in Genital, Rectal, and Blood Compartments in Males vs Females

Sharon M. Seifert[1]; Amie L. Meditz[2]; Jose R. Castillo-Mancilla[3]; Edward M. Gardner[3]; Brandon Klein[1]; Becky Kerr[1]; L. Anthony Guida[1]; Jia-Hua Zheng[1]; Lane R. Bushman[1]; Peter L. Anderson[1]

[1]University of Colorado, Aurora, CO, US; [2]Boulder Community Hospital, Boulder, CO, US; [3]University of Colorado School of Medicine, Aurora, CO, US

526 Effects of Tenofovir/Emtricitabine on Endogenous Deoxyribonucleotide Pools In Vivo

Xinhui Chen[1]; Kevin McAllister[1]; Jia-Hua Zheng[1]; Jose R. Castillo-Mancilla[1]; Amie Meditz[2]; Brandon Klein[1]; Sharon M. Seifert[1]; Lane Bushman[1]; Peter L. Anderson[1]

[1]University of Colorado Anschutz Medical Campus, Aurora, CO, US; [2]Beacon Center of Infectious Diseases, Boulder, CO, US

527 Higher Cell Accumulation and Antiviral Activity of Lopinavir/Ritonavir Nanoparticles

Philip Martin[1]; Tom O. McDonald[2]; Marco Giardiello[2]; Steven P. Rannard[2]; Andrew Owen[1]

[1]University of Liverpool, Liverpool, United Kingdom; [2]University of Liverpool, Liverpool, United Kingdom

528 HIV reservoir targeted antiretroviral nanofabrication facilitates viral clearance

Pavan Puligujja[1]; JoEllyn McMillan[1]; Shantanu Balkundi[2]; Prasanta K. Dash[1]; James Hilaire[1]; Santhi Gorantla[1]; Larisa Poluektova[1]; Xin-Ming Liu[1]; Howard Gendelman[1]

[1]University of Nebraska Medical Center, Omaha, NE, US; [2]Kansas University Innovation and Collaboration, Lawrence, KS, US

529 The Macrophage Proteome Defines the Long Acting Antiretroviral Therapy Cell Depot

Dongwei Guo; Mariluz Araínga; Jayme Horning; Pawel Ciborowski; Xin-Ming Liu; JoEllyn McMillan; Howard Gendelman

University of Nebraska Medical Center, Omaha, NE, US

530 Primary CD4 Subsets Are Similarly Loaded by Tenofovir Alafenamide (TAF)

Christian R. Frey; Yang Liu; Darius Babusis; Adam Palazzo; Adrian S. Ray; Michael D. Miller; Kathryn M. Kitrinos; **Christian Callebaut**

Gilead Sciences, Inc., Foster City, CA, US

Session P-H5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

New Technologies in Assessing Drug Interactions and Systemic and Intracellular Pharmacology

531 Pharmacokinetic Interactions Between Antidiabetics and Efavirenz Using PBPK Modeling

Catia Marzolini[1]; Rajith Rajoli[2]; Luigia Elzi[1]; Manuel Battegay[1]; David Back[2]; Marco Siccardi[2]

[1]University Hospital Basel, Basel, Switzerland; [2]Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom

532 In Silico Simulation of Interaction Between Rifampicin and Boosted Darunavir

Marco Siccardi; Owain Roberts; Rajith Rajoli; Laura Dickinson; Saye Khoo; Andrew Owen; David Back

University of Liverpool, Liverpool, United Kingdom

533 Pharmacogenetics of Pregnancy-Induced Changes in Efavirenz Pharmacokinetics

Adeniyi Olagunju[1]; Oluseye Bolaji[2]; Alieu Amara[1]; Laura Else[1]; Ogechi Okafor[3]; Ebunoluwa Adejuyigbe[2]; Oyigboja Johnson[4]; David Back[1]; Saye Khoo[1]; Andrew Owen[1]

[1]University of Liverpool, Liverpool, United Kingdom; [2]Obafemi Awolowo University, Ile-Ife, Nigeria; [3]Bishop Murray Medical Centre, Makurdi, Nigeria; [4]Catholic Caritas Foundation of Nigeria, Makurdi, Nigeria

534 Antiretroviral Drug Transporters and Metabolic Enzymes in Human Testicular Tissue

Billy Huang[1]; Md. Tozammel Hoque[1]; Mohammad-Ali Jenabian[3]; Kishanda Vyboh[2]; Nancy Sheehan[2]; Pierre Brassard[4]; Maud Bélanger[4]; Nicolas Chomont[5]; Jean-Pierre Routy[2]; Reina Bendayan[1]

[1]University of Toronto, Toronto, Canada; [2]McGill University, Montréal, Canada; [3]Université du Québec à Montréal, Montréal, Canada; [4]Metropolitan Centre of Plastic Surgery, Montréal, Canada; [5]Vaccine and Gene Therapy Institute of Florida, Port St Lucie, FL, US

535 Imaging the Spatial Distribution of Efavirenz in Intact HIV Tissue Reservoirs

Elias P. Rosen[1]; Corbin G. Thompson[2]; Mark T. Bokhart[1]; Craig Sykes[2]; Yuri Fedoriw[2]; Paul Luciw[3]; David C. Muddiman[1]; Angela D.M. Kashuba[2]

[1]North Carolina State University, Raleigh, NC, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]University of California Davis, Davis, CA, US

WEDNESDAY, FEBRUARY 25, 2015

Session P-I1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Drug Development

536 Inhibition of HIV-1 Replication by a Novel Acylguanidine-Based Molecule

Philip Mwimanzi[1]; Ian Tietjen[2]; Aniqa Shahid[1]; Scott C. Miller[2]; David Fedida[2]; Zabrina L. Brumme[1]; Mark Brockman[1]

[1]Simon Fraser University, Burnaby, Canada; [2]University of British Columbia, Vancouver, Canada

537 4′-Ethynyl-2-Fluoro-2′-Deoxyadenosine (EFdA) Has an Extremely High Genetic Barrier, Persistently Exerting Highly Potent Activity Against a Variety of HIV-1 Isolates Including EFdA-Selected HIV-1 Variants

Kenji Maeda[1]; Yuki Takamatsu[1]; Satoru Kohgo[2]; Nicole S. Delino[1]; Simon B. Chang[1]; Kazuhiro Haraguchi[3]; Hiroaki Mitsuya[1]

[1]National Institutes of Health (NIH), Bethesda, MD, US; [2]National Center for Global Health and Medicine, Tokyo, Japan; [3]Nihon Pharmaceutical University, Saitama, Japan

538 GSK2838232, a Second Generation HIV-1 Maturation Inhibitor With an Optimized Virology Profile

Jerry Jeffrey[1]; Ping Wang[1]; Charlene McDanal[1]; Pauline J. Shipper[2]; Kevin Brown[1]; Cristin Galardi[1]; Jun Tang[1]; Monique Nijhuis[2]; Brian Johns[1]

[1]GlaxoSmithKline, Research Triangle Park, NC, US; [2]University of Utrecht, Utrecht, Netherlands

539 Maturation Inhibitor Mechanistic Studies - Differential Inhibition of Gag Polymorphs

Zeyu Lin[1]; Joseph Cantone[1]; Tricia Protack[1]; Dieter Drexler[1]; Beata Nowicka-Sans[1]; Yuan Tian[3]; Zheng Liu[1]; Mark Krystal[1]; Alicia Regueiro-Ren[1]; **Ira B. Dicker**[1]

[1]Bristol-Myers Squibb Co, Wallingford, CT, US; [2]Bristol-Myers Squibb Co, Wallingford, CT, US; [3]Bristol-Myers Squibb Co, Princeton, NJ, US; [4]Bristol-Myers Squibb Co, Wallingford, CT, US

540 Late-Stage Integrase-LEDGF Inhibitors Mode of Action and Acquisition of Resistance

Richard Benarous[1]; Erwann Le Rouzic[1]; Nikki van Bel[2]; Yme Van der Velden[2]; Damien Bonnard[1]; Atze Das[2]; Celine Amadori[1]; Alessia Zamborlini[4]; Stephane Emiliani[3]; Ben Berkhout[2]

[1]Biodim Mutabilis, Romainville, France; [2]Academic Medical centre, Amsterdam, Netherlands; [3]Inserm CNRS, Paris, France; [4]U944 UMR7212, Inserm CNRS, Paris, France

541 BMS-986001: A Promising Candidate for HIV-2 Treatment

Robert A. Smith[1]; Dana Raugi[1]; Kate Parker[1]; Mariah Oakes[1]; Papa Salif Sow[2]; Selly Ba[2]; Moussa Seydi[2]; Geoffrey S. Gottlieb[1]

On behalf of the University of Washington-Dakar HIV-2 Study Group

[1]University of Washington, Seattle, WA, US; [2]CHNU de Fann, Dakar, Senegal

542 Dual Loaded Sustained Release Core-Shell Nanoparticles for Anti-HIV Therapy

Hilliard L. Kutscher[1]; Jessica L. Reynolds[1]; Faithful Makita[2]; Sara DiTursi[1]; Jacob Milling[1]; Jesse Hanchett[1]; Charles C. Maponga[2]; Paras N. Prasad[1]; Gene D. Morse[1]

[1]University at Buffalo, Buffalo, NY, US; [2]University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe

543 Chemical Facilitated Endosomal Storage of Long-Acting Antiretroviral Nanoparticles

Dongwei Guo; **Prasanta K. Dash**; Gang Zhang; Mariluz Arainga; Jaclyn Knibbe; JoEllyn McMillan; Larisa Poluektova; Harris Gelbard; Santhi Gorantla; Howard Gendelman

University of Nebraska Medical Center, Omaha, NE, US

TUESDAY, FEBRUARY 24, 2015

Session P-J1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

ART: Recent Perspectives

544 24-Weeks Virologic Efficacy of Fozivudine in ART-Naïve Patients From Africa

Arne Kroidl[1]; Tessa Lennemann[1]; Frederic Ello[2]; Jimson Mgaya[3]; Raoul Moh[2]; Lucas Maganga[3]; Serge P. Eholié[2]; Pierre-Marie Girard[4]; Friedrich von Massow[5]; Christine Danel[6]

[1]Medical Center of the University of Munich (LMU), Munich, Germany; [2]CHU de Treichville, Abidjan, Côte d'Ivoire; [3]NIMR–Mbeya Medical Research Center, Mbeya, United Republic of Tanzania; [4]University Hospital Saint-Antoine, Paris, France; [5]Institute for Life Sciences and Environment GmbH, Heidelberg, Germany; [6]Programme PAC-CI, ANRS, Abidjan, Côte d'Ivoire

545 Attachment Inhibitor Prodrug BMS–663068 in ARV-Experienced Subjects: Week 48 Analysis

Melanie Thompson[1]; Jay Lalezari[2]; Richard Kaplan[3]; Yvette Pinedo[4]; Otto Sussman Pena[5]; Pedro Cahn[6]; David A. Stock[7]; Samit R. Joshi[7]; George J. Hanna[8]; Max Lataillade[7]

[1]AIDS Research Consortium of Atlanta, Atlanta, GA, US; [2]Quest Clinical Research, San Francisco, CA, US; [3]Desmond Tutu HIV Foundation, Cape Town, South Africa; [4]Asociacion Civil Via Libre, Lima, Peru; [5]Asistencia Cientifica de Alta Complejidad SAS, Bogotá, Colombia; [6]Fundacion Huesped, Buenos Aires, Argentina; [7]Bristol-Myers Squibb, Wallingford, CT, US; [8]Bristol-Myers Squibb, Princeton, NJ, US

546 Delay in Antiretroviral Therapy Is Not Associated With Increased Virologic Failure

Ashita S. Batavia[1]; Patrice Severe[2]; Marc Antoine Jean Juste[2]; Rode Secours[2]; Daphne C. Bernard[2]; William J. Pape[2]; Daniel Fitzgerald[1]

[1]Weill Cornell Medical College, New York, NY, US; [2]GHESKIO Center, Port-au-Prince, Haiti

547 Effects of Quadruple First-Line ART on Mucosal Immunity

Sergio Serrano-Villar[1]; Talía Sainz[2]; Surinder Mann[3]; Zhong-Min Ma[3]; Christopher Miller[3]; Netanya S. Utay[4]; Basile Siewe[5]; Tae Wook-Chun[6]; Paolo Troia-Cancio[3]; David Asmuth[3]

[1]University Hospital Ramón y Cajal, Madrid, Spain; [2]University Hospital Gregorio Marañón, Madrid, Spain; [3]University of California Davis, Sacramento, CA, US; [4]University of Texas, Galveston, TX, US; [5]Rush University Medical Center, Chicago, IL, US; [6]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

548 Maraviroc-Dependent Pharmacologic Effects on Viral Decay and Immune Recovery in GALT

Corbin Thompson[1]; Tae Wook Chun[2]; Craig Sykes[1]; Zhing-Min Ma[4]; Christopher Miller[4]; Surinder Mann[3]; Richard Pollard[3]; Angela Kashuba[1]; David Asmuth[3]

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, US; [2]Division of AIDS, NIAID, NIH, Bethesda, MD, US; [3]University of California Davis Medical Center, Davis, CA, US; [4]University of California Davis, Davis, CA, US

549 Maraviroc Induces HIV Production in RCT and In Vitro, Potentially via the NFkB Pathway

Jori Symons[1]; Ward de Spiegelaere[2]; Annemarie Wensing[1]; Julia Drylewicz[3]; Ananja Middel[4]; Andy I. Hoepelman[4]; Kiki Tesselaar[3]; Linos Vandekerckhove[2]; Steven F. van Lelyveld[4]; **Monique Nijhuis**[1]

[1]University Medical Center Utrecht, Utrecht, Netherlands; [2]Ghent University, Ghent, Belgium; [3]University Medical Centre Utrecht, Utrecht, Netherlands; [4]University Medical Centre Utrecht, Utrecht, Netherlands

550 Consistency of Dolutegravir Treatment Difference in HIV+ Treatment Naives at Week 96

Catherine M. Granier[1]; **Robert Cuffe**[2]; Louise Martin-Carpenter[3]; Kimberly Y. Smith[3]; Clare Brennan[4]; Keith Pappa[4]; Brian Wynne[4]; Steve Almond[5]; Naomi Givens[1]; Michael Aboud[2]

[1]GlaxoSmithKline, Uxbridge, United Kingdom; [2]ViiV Healthcare, London, United Kingdom; [3]ViiV Healthcare, Research Triangle Park, NC, US; [4]GlaxoSmithKline, Research Triangle Park, NC, US; [5]GlaxoSmithKline, Mississauga, Canada

551 Predictors of HIV RNA Suppression on Darunavir/Ritonavir Monotherapy in the MONET and PROTEA Trials

Diego Ripamonti[2]; Ralph DeMasi[3]; **Andrew M. Hill**[1]; Ceyhun Bicer[4]; Christiane Moecklinghoff[5]

[1]Chelsea and Westminster Hospital, London, United Kingdom; [2]A.O. Papa Giovanni XXIII, Bergamo, Italy; [3]Janssen Pharmaceuticals, Inc., Titusville, NJ, US; [4]Janssen Pharmaceuticals, Inc., Beerse, Belgium; [5]Janssen Pharmaceuticals, Inc., Neuss, Germany

552 Second-Line Treatment in Sub-Saharan Africa: Week 144 Follow-up of the EARNEST Trial

James G. Hakim[1]; Jennifer Thompson[2]; Cissy M. Kityo[3]; Sarah Walker[2]; Joep van Oosterhout[4]; Anne Hoppe[2]; Andrew D. Kambugu[5]; Peter Mugyenyi[3]; Nicholas Paton[6]
On behalf of the EARNEST Trial Team

[1]University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe; [2]University College London, London, United Kingdom; [3]Joint Clinical Research Centre, Kampala, Uganda; [4]Dignitas, Zomba, Zomba, Malawi; [5]Infectious Disease Institute, Kampala, Uganda; [6]National University of Singapore, Singapore, Singapore; [7]MRC Clinical Trials Unit at University College London, London, United Kingdom

553 Withdrawing Inactive NRTIs in Subjects With Suppressed Viremia: A Randomized Trial

Josep M. Llibre[1]; Hortensia Alvarez[8]; Antonio Antela[2]; Jessica Toro[1]; Juan González-Moreno[3]; M Jesús Perez-Elias[4]; Arkaitz Imaz[5]; Mar Masià[6]; Manel Crespo[7]; Bonaventura Clotet[1]

[1]Univ Hosp Germans Trias, Badalona, Spain; [2]Hospital Clínico Universitario, Santiago de Compostela, Spain; [3]Hospital Son Llàtzer, Mallorca, Spain; [4]Hospital Ramón y Cajal, IRYCIS, Madrid, Spain; [5]Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain; [6]Hospital Universitario de Elche, Elche, Spain; [7]Hospital Universitari Vell d'Hebró, Barcelona, Spain; [8]Complejo Universitario de Ferrol, A Coruña, Spain

554LB Cabotegravir and Rilpivirine As 2-Drug Oral Maintenance Therapy: LATTE W96 Results

David A. Margolis[1]; Cynthia C. Brinson[2]; Graham H. Smith[3]; Jerome de Vente[4]; Debbie P. Hagins[5]; Sandy K. Griffith[1]; Marty H. St. Clair[1]; Kimberly Y. Smith[6]; Peter E. Williams[7]; William R. Spreen[1]

[1]GlaxoSmithKline, Durham, NC, US; [2]Central Texas Clinical Research, Austin, TX, US; [3]Maple Leaf Medical Clinic, Toronto, Canada; [4]Living Hope Foundation, Long Beach, CA, US; [5]Chatham County Health Department, Savannah, GA, US; [6]ViiV Healthcare, Durham, NC, US; [7]Janssen Pharmaceuticals, Inc, Beerse, Belgium

Session P-K1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

ART: Adherence, Adherence, Adherence

555 Self-Reported Versus Blood-Tested ART Intake to Estimate ART Coverage in South Africa

Helena Huerga[1]; Gilles Van Cutsem[2]; Lubbe Wiesner[3]; Malika Bouhenia[1]; Jihane Ben Farhat[1]; Emmanuel Fajardo[2]; Ruggero G. Giuliani[2]; David Maman[1]; Thomas Ellman[2]; Jean-François Etard[1]

[1]Epicentre, Paris, France; [2]Médecins Sans Frontières, Cape Town, South Africa; [3]University of Cape Town, Cape Town, South Africa

556 Real-Time Electronic Adherence Monitoring and Risk of Viral Rebound

Jessica E. Haberer[1]; Nicholas Musinguzi[2]; Mark Siedner[1]; Yap Boum[3]; Peter W. Hunt[4]; Jeffrey Martin[4]; David R. Bangsberg[1]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]Mbarara University of Science and Technology, Mbarara, Uganda; [3]Médecins Sans Frontières, Mbarara, Uganda; [4]University of California San Francisco, San Francisco, CA, US

557 Determinants of Adherence to Antiretroviral Therapy Differ Between Africa and Asia

Rimke Bijker[1]; Awachana Jiamsakul[2]; Margaret Siwale[3]; Sasisopin Kiertiburanakul[4]; Cissy M. Kityo[5]; Praphan Phanuphak[6]; Tobias F. Rinke de Wit[1]; Oon Tek Ng[7]; Raph L. Hamers[1]; PASER-TASER Cohort Collaboration[1]
PASER-TASER Cohort Collaboration

[1]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands; [2]The Kirby Institute, Sydney, Australia; [3]Lusaka Trust Hospital, Lusaka, Zambia; [4]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [5]Joint Clinical Research Centre, Kampala, Uganda; [6]HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [7]Tan Tock Seng Hospital, Novena, Singapore

558 Retention on Antiretroviral Therapy by Sex and Pregnancy Status in a Large Cohort of HIV-Infected Patients in Rural Nigeria

Usman I. Gebi[2]; Meridith Blevins[1]; Mukhtar Y. Muhammad[2]; C. William Wester[1]; Muktar H. Aliyu[1]

[1]Vanderbilt University, Nashville, TN, US; [2]Friends for Global Health Initiative Nigeria, Abuja, Nigeria

559 Randomised Controlled Trial of Text-Message Dosing Reminders in Patients Starting ART

Catherine Orrell[1]; Karen Cohen[1]; Katya Mauff[1]; David R. Bangsberg[2]; Gary Maartens[1]; Robin Wood[1]

[1]University of Cape Town, Cape Town, South Africa; [2]Harvard Medical School, Boston, MA, US

560 Socioeconomic Factors and Virological Rebound: A Prospective UK Cohort Study

Lisa S. Burch[1]; Colette Smith[1]; Jane Anderson[3]; Lorraine Sherr[1]; Alison Rodger[1]; Richard Gilson[1]; Jonathan Elford[2]; Andrew N. Phillips[1]; Margaret Johnson[4]; Fiona Lampe[1]
ASTRA (Antiretrovirals, Sexual Transmission Risk and Attitudes)

[1]University College London, London, United Kingdom; [2]City University London, London, United Kingdom; [3]Homerton University Hospital NHS Foundation Trust, London, United Kingdom; [4]Royal Free London NHS Foundation Trust, London, United Kingdom

Session P-K2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

ART: Monitoring and Biomarkers

561 New Marker of Standard-of-ART Care: Percentage of Time on cART With Suppressed HIV-RNA

Kamilla G. Laut[1]; Leah C. Shepherd[4]; Court Pedersen[2]; Jürgen Rockstroh[3]; Helen Sambatakou[5]; Dzmitry Paduta[6]; Jens D. Lundgren[1]; Amanda Mocroft[4]; Ole Kirk[1]; EuroSIDA in EuroCoord[1]
on behalf of EuroSIDA in EuroCoord

[1]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [2]Odense University Hospital, Odense, Denmark; [3]University Hospital Bonn, Bonn, Germany; [4]University College London, London, United Kingdom; [5]Hippokration General Hospital, University of Athens, Athens, Greece; [6]Gomel Regional Centre for Hygiene, Gomel, Belarus

562 Viremia Copy Years and Its Impact on Risk of Clinical Progression According to Shape

Alessandro Cozzi-Lepri[1]; Antonella Cingolani[2]; Andrea Antinori[3]; Andrea De Luca[4]; Cristina Mussini[5]; Stefano Rusconi[6]; Carmela Pinnetti[3]; Massimo Galli[6]; Antonella Castagna[8]; Antonella d'Arminio Monforte[7]

[1]University College London, London, United Kingdom; [2]Sacro Cuore University, Roma, Italy; [3]INMI Spallanzani, Roma, Italy; [4]University of Siena, Siena, Italy; [5]University of Modena, Modena, Italy; [6]Luigi Sacco University Hospital, Milano, Italy; [7]S. Paolo Hospital, Milano, Italy; [8]San Raffaele Scientific Institute, Milano, Italy

563 Monitoring and Switching of Antiretroviral Therapy in Sub-Saharan Africa

Andreas D. Haas[1]; Olivia Keiser[1]; François Dabis[2]; Mary-Ann Davies[3]; Rosalind M. Parkes-Ratanshi[4]; Steven J. Reynolds[5]; Kara Wools-Kaloustian[6]; Gilles Wandeler[1]; Matthias Egger[1]
IeDEA East, West and Southern Africa

[1]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland; [2]Université Bordeaux, Bordeaux, France; [3]University of Cape Town, Cape Town, South Africa; [4]Makerere University College of Health Sciences, Makerere, Uganda; [5]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US; [6]Indiana University, Indianapolis, IN, US

564 Virological Factors Associated With Outcome of Dual MVC/RAL Therapy (ANRS-157 Trial)

Cathia Soulie[1]; Lambert Assoumou[2]; Melanie Darty[3]; Christophe Rodriguez[3]; Gilles Peytavin[4]; Marc-Antoine Valantin[5]; Dominique Costagliola[2]; Christine Katlama[5]; Vincent Calvez[1]; Anne-Genevieve Marcelin[1]

[1]Hôpital Pitié Salpêtrière, Paris, France; [2]INSERM/UPMC, Paris, France; [3]APHP Mondor, Creteil, France; [4]APHP Bichat, Paris, France; [5]Hôpital Saint-Louis, APHP, Université Paris Diderot, Paris, France

565 D-dimer Doesn't Return to Pre-HIV Levels After Therapy and Is Linked With HANA Events

Matthew S. Freiberg[2]; Ionut Bebu[4]; Russell Tracy[3]; Jason F. Okulicz[1]; Anuradha Ganesan[1]; Adam Armstrong[5]; Thomas O'Bryan[1]; **Brian K. Agan**[1]
IDCRP HIV Working Group

[1]Uniformed Services University of the Health Sciences, North Bethesda, MD, US; [2]Vanderbilt University Medical Center, Nashville, TN, US; [3]University of Vermont College of Medicine, Burlington, VT, US; [4]The George Washington University, Rockville, MD, US; [5]US Naval Medical Research Unit No. 6 Peru, Lima, Peru

566 Virological Responses to Lamivudine and Emtricitabine in the Nationwide ATHENA Cohort

Casper Rokx[1]; Azzania Fibriani[1]; David A. van de Vijver[1]; Annelies Verbon[1]; Martin Schutten[1]; Luuk Gras[2]; Bart J. Rijnders[1]
On behalf of the Dutch HIV Monitoring Foundation

[1]Erasmus University Medical Center, Rotterdam, Netherlands; [2]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands

567 Prevalence and Risk Factors of Multiple Micronutrient Deficiencies Pre- and Post-ART

Rupak Shivakoti[1]; Parul Christian[2]; Nikhil Gupte[1]; Cecilia Kanyama[3]; Sima Berendes[4]; Javier Lama[5]; Richard Semba[1]; Thomas Campbell[6]; Amita Gupta[1]
NWCS 319 and PEARLS Study Team

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]University of North Carolina Project–Malawi, Lilongwe, Malawi; [4]Malawi College of Medicine-Johns Hopkins University Research Project, Blantyre, Malawi; [5]Asociacion Civil Impacta Salud y Educacion, Lima, Peru; [6]University of Colorado School of Medicine, Aurora, CO, US

568 Detection of HIV RNA and DNA in Anal Swabs of HIV Infected Men Having Sex With Men

Julian Storim[1]; **Jens Verheyen**[1]; Eva Wolff[1]; Lewin Eisele[1]; Jeremias Wohlschläger[2]; Peter-Michael Rath[1]; Evelyn Heintschel von Heinegg[1]; Dirk Schadendorf[1]; Stefan Esser[1]

[1]University Hospital Essen, University Duisburg-Essen, Essen, Germany; [2]University Hospital Essen, Essen, Germany

WEDNESDAY, FEBRUARY 25, 2015

Session P-K3 Poster Session **Poster Hall**
2:30 pm – 4:00 pm

ART: Immunologic Response—The Good and The Bad

569 Reference Curves for CD4 Response to Antiretroviral Treatment in HIV-1–Infected Naïve Patients

Rodolphe Thiebaut
On behalf of the Standard Reference Distribution of CD4 Working Group in COHERE in EuroCoord

Bordeaux University, Bordeaux, France

570 Comparing Immunological Failure Definitions, Using Tanzanian National HIV Data

Fiona Vanobberghen[1]; Bonita K. Kilama[2]; Alison Wringe[1]; Angela Ramadhani[2]; Basia Zaba[1]; Donan Mmbando[3]; Jim Todd[1]

[1]London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]National AIDS Control Program, Dar es Salaam, United Republic of Tanzania; [3]Ministry of Health & Social Welfare, Dar es Salaam, United Republic of Tanzania

571 Delaying Second-Line Therapy After First-Line Failure: Moderating Effect of CD4 Count

Julia K. Rohr[1]; Prudence Ive[2]; Rebecca H. Berhanu[3]; Kate Shearer[2]; Mhairi Maskew[2]; Lawrence Long[2]; Ian Sanne[2]; Matthew P. Fox[1]

[1]Boston University School of Public Health, Boston, MA, US; [2]University of Witswatersrand, Johannesburg, South Africa; [3]Right to Care, Johannesburg, South Africa

572 Rapid Progression Hinders the Recovery of CD4 + T Cells Following Initiation of cART

Inma Jarrin
On behalf of the CASCADE Collaboration within EUROCOORD

Instituto de Salud Carlos III, Madrid, Spain

573 Increase in CD4 Counts at Presentation to ART Care Among Urban HIV Clinics in Uganda

ELIZABETH K. NALINTYA[1]; Agnes N. Kiragga[1]; Edison Katunguka[2]; Henry W. Nabeta[1]; Joanita Kigozi[1]; Yukari Manabe[4]; David R. Boulware[2]; Jon Kaplan[3]; David B. Meya[1]

[1]Infectious Diseases Institute, Kampala Uganda, Kampala, Uganda; [2]University of Minnesota, Minneapolis, MN, US; [3]CDC Center for Global Health, Division of Global AIDS/HIV, Atlanta, GA, US; [4]Johns Hopkins University, Baltimore, MD, US

574 Implications of Poor CD4 Recovery During HIV Suppressive ART in Sub-Saharan Africa

Marieke E. de Pundert[1]; Tamara Sonia Boender[1]; Raph L. Hamers[1]; Kim Sigaloff[1]; Cissy M. Kityo[2]; Alani S. Akanmu[3]; Maureen Wellington[4]; Tobias F. Rinke de Wit[1]; Pascale Ondoa[1]
Pan African Studies to Evaluate Resistance (PASER) studygroup

[1]Amsterdam Institute for Global Health and Development, Brasschaat, Belgium; [2]Joint Clinical Research Centre Kampala, Kampala, Uganda; [3]Lagos University Teaching Hospital, Lagos, Nigeria; [4]Newlands Clinic, Harare, Zimbabwe

575 Better CD4/CD8 Restoration in First-Line HIV-Infected CMV-Seronegative Patients

Isabelle Poizot-Martin[1]; Clotilde Allavena[2]; Claudine Duvivier[3]; Carla E. Cano[1]; Francine Guillouet de Salvador[4]; David Rey[5]; Lise Cuzin[6]; Antoine Cheret[7]; Bruno Hoen[8]
On behalf of the Dat'AIDS Group

[1]Aix-Marseille Univ, APHM Hôpital Sainte-Marguerite, Marseille, France; [2]CHU Hotel Dieu, Nantes, France; [3]APHP–Hopital Necker–Université Paris Descartes–IHU Imagine, Paris, France; [4]CHU Archet 1, Nice, France; [5]Hôpitaux Universitaires Strasbourg, Strasbourg, France; [6]Regional Coordination for HIV, Toulouse, France; [7]Hospital Tourcoing, Tourcoing, France; [8]University Medical Center of Guadeloupe, Guadeloupe, France; [9]The Dat'AIDS Group, Nice, France

576 CD4 Response in Treatment-Naïve HIV-2–Infected Patients: The IeDEA West Africa Cohort

Eric Balestre[1]; Koumavi K. Ekouevi[2]; Boris Tchounga[2]; Serge P. Eholié[3]; Eugène Messou[4]; Adrien Sawadogo[5]; Rodolphe Thiebaut[1]; Margaret T. May[6]; Jonathan A. Sterne[6]; François Dabis[1]

[1]Univ Bordeaux, ISPED, Centre Inserm U897-Epidemiologie-Biostatistique, Bordeaux, France; [2]Programme PAC-CI, Centre Hospitalier Universitaire de Treichville, Abidjan, Côte d'Ivoire; [3]Service de Maladies Infectieuses et Tropicales, Centre Hospitalier Universitaire de Treichville, Abidjan, Côte d'Ivoire; [4]Centre de Prise en Charge de Recherche et de Formation, Hôpital Yopougon Attié, Abidjan, Côte d'Ivoire; [5]Institut Supérieur des Sciences de la Santé, Université Polytechnique de Bobo-Dioulasso, Bobo-Dioulasso, Burkina Faso; [6]School of Social and Community Medicine, Bristol University, Bristol, United Kingdom

Session P-K4 Poster Session **Poster Hall**
2:30 pm – 4:00 pm

ART: Mortality

577 Mortality and Retention After 12 Months in a Cohort of Patients Initiated With the New WHO Recommendations in Uganda

John Ssali; Juan Gonzalez Perez; Jonathan Ikapule; Lydia Buzaalirwa; Kate Ssamula; Augustine Lubanga; Sulaiman Kawooya; Monday Busuulwa; Penninah Lutung Amor; **Michael Wohlfeiler**

AIDS Healthcare Foundation, Kampala, Uganda

578 Effect of ART on Mortality Generalized to Newly HIV-Diagnosed Persons in the USA

Catherine R. Lesko[1]; Stephen R. Cole[1]; H. Irene Hall[3]; Michael J. Mugavero[2]

[1]University of North Carolina, Chapel Hill, NC, US; [2]University of Alabama at Birmingham, Birmingham, AL, US; [3]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

579 Association of CD4:CD8 With Cause-Specific Mortality in Patients on Long-Term ART

Margaret T. May[1]; Adam Trickey[1]; Dominique Costagliola[6]; Peter Reiss[4]; Santiago Moreno[5]; John Gill[3]; Colette Smith[2]; Suzanne M. Ingle[1]; Jonathan A. Sterne[1]
On behalf of the Antiretroviral Therapy Cohort Collaboration (ART-CC)

[1]University of Bristol, Bristol, United Kingdom; [2]University College London, London, United Kingdom; [3]University of Calgary, Calgary, Canada; [4]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [5]Hospital Ramón y Cajal, Madrid, Spain; [6]UMR S 1136, Inserm et Sorbonne Universités, Université Pierre et Marie Curie, Paris, France

580 Outcomes of First ART in Latino Populations in North America and Latin America

Carina T. Cesar[1]; Mark J. Giganti[2]; Bryan E. Shepherd[2]; Richard Moore[3]; Keri N. Althoff[3]; Sonia Napravnik[4]; Angel M. Mayor[5]; Catherine Mc Gowan[2]; Pedro E. Cahn[1]

[1]Fundacion Huesped, Buenos Aires, Argentina; [2]Vanderbilt University, Nashville, TN, US; [3]Johns Hopkins University, Baltimore, MD, US; [4]University of North Carolina, Chapel Hill, NC, US; [5]Retrovirus Research Center, Bayamon, US

581 WITHDRAWN

582 Impact of Specific Antiretroviral Drugs on Non-AIDS Mortality; the D:A:D Study

Camilla I. Hatleberg[1]; Lene Ryom[1]; Andrew N. Phillips[2]; Amanda Mocroft[2]; Peter Reiss[3]; Matthew Law[4]; Rainer Weber[5]; François Dabis[6]; Jens D. Lundgren[1]; Colette Smith[2]
On behalf of the D:A:D Study group

[1]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [2]University College London, London, United Kingdom; [3]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; [4]University of New South Wales, Sydney, Australia; [5]University Hospital Zurich, Zurich, Switzerland; [6]University of Bordeaux, Bordeaux, France

583 HIV-Related Causes of Death in the Era of Antiretroviral Therapy: Analysis of Verbal Autopsy Data

Clara Calvert[1]; Zehang Li[2]; Tyler McCormick[2]; Alison Price[1]; Kobus Herbst[4]; Denna Michael[3]; Estelle McLean[1]; Basia Zaba[1]; Samuel Clark[2]
On behalf of the ALPHA network

[1]London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]University of Washington, Seattle, WA, US; [3]National Institute for Medical Research, Mwanza, United Republic of Tanzania; [4]Africa Centre for Health and Population Studies, Mtubatuba, South Africa

584 Facility-Level Factors Associated With Mortality of Patients on ART: A Retrospective Cohort Study in Kenya, 2007-2012

Emily A. Dansereau[1]; Allen Roberts[1]; Herbert C. Duber[1]; Gregoire Lurton[1]; Brendan DeCenso[2]; Thomas Odeny[1]; Samuel Masters[3]; Roy Burstein[1]; Pamela Njuguna[1]; Emmanuela Gakidou[1]

[1]University of Washington, Seattle, WA, US; [2]RTI International, Raleigh, NC, US; [3]University of North Carolina, Chapel Hill, NC, US

THURSDAY, FEBRUARY 26, 2015

Session P-L1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HIV Drug Resistance: Mechanisms and Mutations

585 Structural Basis of Inhibition and Resistance Mechanism to EFdA, a Highly Potent NRTI

Zhe Li[1]; Karen Kirby[1]; Bruno Marchand[1]; Michailidis Eleftherios[1]; Eiichi Kodama[2]; Hiroaki Mitsuya[3]; Michael Parniak[4]; Stefan Sarafianos[1]

[1]University of Missouri, Columbia, MO, US; [2]Tohoku University, Sendai, Japan; [3]National Institutes of Health, Division of AIDS, Bethesda, MD, US; [4]University of Pittsburgh, Pittsburgh, PA, US

586 Structural Basis and Distal Effects of Gag Substrate Coevolution in Drug Resistance to HIV-1 Protease

Kuan-Hung Lin; Celia A. Schiffer

University of Massachusetts Medical School, Worcester, MA, US

587 Influence of Codon Pair Usage in the Evolvability of HIV-1

Maria Nevot; Cristina Andrés; Mariona Parera; Glòria Martrus; Miguel Ángel Martínez

IrsiCaixa Institute for AIDS Research, Badalona, Spain

588 Four Amino Acid Changes in HIV-2 Protease Confer Class-Wide PI Susceptibility

Dana N. Raugi[1]; Robert A. Smith[1]; Matthew Coyne[1]; Julia Olson[1]; Kara Parker[1]; Selly Ba[2]; Papa Salif Sow[2]; Moussa Seydi[2]; Geoffrey S. Gottlieb[1]
University of Washington-Dakar HIV-2 Study Group

[1]University of Washington School of Medicine, Seattle, WA, US; [2]Centre Hospitalier National Universitaire de Fann, Universite Cheikh Anta Diop de Dakar, Dakar, Senegal

589 Enhanced Neutralization of HIV-1 With Fusion Inhibitor Resistant Mutations

Muntasir Alam[1]; Takeo Kuwata[1]; Kristel P. Ramirez[1]; Yasuhiro Maruta[1]; Kazuki Tanaka[1]; Kazuya Shimura[2]; Shinya Oishi[2]; Nobutaka Fujii[2]; Masao Matsuoka[2]; Shuzo Matsushita[1]

[1]Kumamoto University, Kumamoto, Japan; [2]Kyoto University, Kyoto, Japan

590 Mutations at the Bottom of the Phe43 Cavity Are Responsible for Cross-Resistance to NBD Analogues

Shigeyoshi Harada[1]; Yu Irahara[2]; Samatchaya Boonchawalit[1]; Mai Goryo[1]; Hirokazu Tamamura[2]; Tetsuro Matano[1]; Shuzo Matsushita[3]; Kazuhisa Yoshimura[1]

[1]National Institute of Infectious Diseases, Shinjuku, Japan; [2]Tokyo Medical and Dental University, Chiyoda, Japan; [3]Kumamoto University, Kumamoto, Japan

591 SIV_{mac239} Integrase as a Model of HIV Drug Resistance Against Integrase Inhibitors

Said Hassounah[1]; Thibault Mesplede[1]; Maureen Oliveira[1]; Peter K. Quashie[1]; Daniela Moisi[1]; Paul A. Sandstrom[2]; Mark A. Wainberg[1]; Bluma Brenner[1]

[1]McGill University, Montréal, Canada; [2]National HIV and Retrovirology Laboratory, National Microbiology Laboratory, Public Health Agency of Canada, Ottawa, Canada

592 Within-Run Cross-Contamination in Deep Sequencing Applications on the Illumina MiSeq

Chanson J. Brumme; Winnie Dong; Celia K. Chui; Richard Liang; Art F. Poon; Richard Harrigan

BC Centre for Excellence in HIV/AIDS, Vancouver, Canada

593 Analysis of Resistance Haplotypes Using Primer IDs and Next Gen Sequencing of HIV RNA

Valerie F. Boltz[1]; Jason Rausch[1]; Wei Shao[2]; Charles Coomer[1]; John W. Mellors[3]; Mary Kearney[1]; John M. Coffin[4]

[1]National Institutes of Health (NIH), Frederick, MD, US; [2]Leidos, Frederick, MD, US; [3]University of Pittsburgh, Pittsburgh, PA, US; [4]Tufts University, Boston, MA, US

Session P-L2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HIV Subtypes and Resistance

594 HIV-1 Subtype Influences the Pathways of Genotypic Resistance to Integrase Inhibitors

Tomas J. Doyle[1]; David Dunn[4]; Rolf Kaiser[3]; Erasmus Smit[10]; Anne-Genevieve Marcelin[5]; Carmen de Mendoza[6]; Javier Martínez-Picado[9]; Federico Garcia[7]; Francesca Ceccherini-Silberstein[8]; Anna Maria Geretti[2]
CORONET study group

[1]King's College London, London, United Kingdom; [2]University of Liverpool, Liverpool, United Kingdom; [3]University of Cologne, Cologne, Germany; [4]University College London, London, United Kingdom; [5]Hôpital Pitié Salpetriere, APHM, Paris, France; [6]Hospital Carlos III, Madrid, Spain; [7]University Hospital San Cecilio, Granada, Spain; [8]University of Rome Tor Vergata, Rome, Italy; [9]Institut de Recerca de la Sida, Barcelona, Spain; [10]Birmingham Heartlands Hospital, Birmingham, United Kingdom

595 Differences in Resistance Mutations in Non-B Subtypes at First-Line Failure in Africa

Cissy M. Kityo[1]; Sarah Walker[2]; Immaculate Nankya[1]; Anne Hoppe[2]; Jennifer Thompson[2]; Silvia Bertagnolio[3]; Philippa Easterbrook[3]; Peter Mugyenyi[1]; Nicholas Paton[4]
On behalf of the EARNEST Trial Team

[1]Joint Clinical Research Centre, Kampala, Uganda; [2]MRC Clinical Trials Unit at University College London, London, United Kingdom; [3]World Health Organization, Geneva, Switzerland; [4]Yong Loo Lin School of Medicine, Singapore, Singapore

596 K65R Detected More Frequently in HIV-1 Subtype C Viruses at Virological Failure

Erasmus Smit[1]; **Ellen White**[7]; Duncan Clark[4]; Duncan Churchill[2]; Hongyi Zhang[6]; Simon Collins[5]; Deenan Pillay[3]; Anna Tostevin[7]; David Dunn[7]
UKHDRD and UKCHIC

[1]Public Health England, Birmingham, United Kingdom; [2]Brighton and Sussex Hospitals NHS Trust, Brighton, United Kingdom; [3]University of KwaZulu-Nata and University College London, London, United Kingdom; [4]St Batholomew's and the London NHS Trust, London, United Kingdom; [5]HIV i-Base, London, United Kingdom; [6]Addenbrooke's Hospital, Cambridge, United Kingdom; [7]University College London, London, United Kingdom

597 Viral Failure and High K65R in Kenyan Patients on Tenofovir-Based First-Line Therapy

Katherine C. Brooks[2]; Lameck Diero[1]; Allison Delong[2]; Maya Balamane[2]; Marissa Reitsma[2]; Emmanuel Kemboi[3]; Millicent Orido[3]; Mia Coetzer[2]; Joseph Hogan[2]; Rami Kantor[2]

[1]Moi University, Eldoret, Kenya; [2]Brown University, Providence, RI, US; [3]Academic Model Providing Access to Healthcare, Eldoret, Kenya

Session P-L3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Transmitted HIV Drug Resistance: Assessing the Threat

598 Large NNRTI-Resistant Transmission Cluster in Injection Drug Users From Saskatchewan

Alexander Wong[1]; Jaspreet Kambo[1]; Richard Harrigan[2]; Art F. Poon[2]; Jeffrey B. Joy[2]

[1]University of Saskatchewan, Regina, Canada; [2]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada

599 Transmitted Drug Resistance and Time of HIV Infection, New York State, 2006-2013

Zhengyan Wang[1]; Emily Walits[2]; Daniel E. Gordon[1]; Bridget J. Anderson[1]; Deepa Rajulu[1]; Ling Wang[1]; Lou C. Smith[1]

[1]New York State Department of Health, Albany, NY, US; [2]University at Albany, School of Public Health, Albany, NY, US

600 Transmitted HIV Drug Resistance Among Early Infected Persons in San Diego, California

Theppharit Panichsillapakit[1]; David M. Smith[2]; Joel Wertheim[2]; Douglas D. Richman[2]; Susan Little[2]; Sanjay Mehta[2]

[1]Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [2]University of California San Diego (UCSD), La Jolla, CA, US

601 HIV Molecular Epidemiology and Transmitted Drug Resistance in the Mesoamerican Region

Claudia Garcia-Morales[1]; Santiago Avila-Rios[1]; Daniela Tapia-Trejo[1]; Carlos Mejía-Villatoro[2]; Juan M Pascale[3]; Guillermo Porras-Cortes[5]; Ivette Lorenzana[4]; Elsa Palou[4]; Marvin Manzanero[6]; Gustavo Reyes-Terán[1]

[1]National Institute of Respiratory DIsease, Mexico City, Mexico; [2]Roosevelt Hospital, Guatemala City, Guatemala; [3]Gorgas Memorial Institute for Health Studies, Panama City, Panama; [4]Universidad Nacional Autónoma de Honduras, Tegucigalpa, Honduras; [5]Vivian Pellas Metropolitan Hospital, Managua, Nicaragua; [6]Ministry of Health, Belize City, Belize

602 Temporal Trends of Transmitted HIV Drug Resistance Following Seroconversion

Ashley Olson[1]; Claudia Kucherer[3]; Anders Sönnerborg[4]; Carmen de Mendoza[5]; Robert Zangerle[6]; Maria Prins[9]; John Gill[2]; Anne-Marte Bakken Kran[7]; Dimitrios Paraskevis[8]; Kholoud Porter[1]
for CASCADE collaboration in EuroCoord

[1]University College London, London, United Kingdom; [2]University of Calgary, Alberta Health Services, Calgary, Canada; [3]Robert Koch Institute, Berlin, Germany; [4]Karolinska Institutet, Stockholm, Sweden; [5]Puerta de Hierro Research Institute and University Hospital, Madrid, Spain; [6]Innsbruck Medical University, Innsbruck, Austria; [7]Oslo University Hospital, Oslo, Norway; [8]University of Athens, Athens, Greece; [9]Public Health Service of Amsterdam, Amsterdam, Netherlands

603 Increase in HIV Primary Drug Resistance in a Demographic Surveillance Area in Rural KwaZulu-Natal South Africa

Justen Manasa; Siva Danaviah; Frank Tanser; Sureshnee Pillay; Hloniphile Mthiyane; Eduan Wilkinson; Deenan Pillay; **Tulio de Oliveira**

University of KwaZulu-Natal, Durban, South Africa

Session P-L4 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HIV Drug Resistance: Global Perspective and Clinical Implications

604 A Clinical Prediction Rule for PI Resistance in Resource-Limited Settings

Karen Cohen[1]; Annemie Stewart[1]; Andre P. Kengne[1]; Rory F. Leisegang[1]; Marla Coetsee[2]; Shavani Maharaj[2]; Liezl Dunn[2]; Graeme Meintjes; Gert U. van Zyl[3]; Gary Maartens[1]

[1]University of Cape Town, Cape Town, South Africa; [2]Aid for AIDS Management (Pty) Ltd, Cape Town, South Africa; [3]University of Stellenbosch, Cape Town, South Africa

605 Baseline Low-Frequency HIV-1 Variants Do Not Predict Virologic Failure to RPV/FTC/TDF

Danielle P. Porter[1]; Martin Däumer[2]; Alexander Thielen[2]; Michael D. Miller[1]; Kirsten L. White[1]

[1]Gilead Sciences, Inc., Foster City, CA, US; [2]Seq-IT GmbH & Co KG, Kaiserslautern, Germany

606 High Rates of Early Virologic Failure in a Cohort of Tanzanian HIV-Infected Adults

Claudia A. Hawkins[1]; Nzovu Ulenga[2]; Enju Liu[3]; Said Aboud[4]; Ferdinand Mugusi[4]; Guerino Chalamilla[2]; David Sando[2]; Eric Aris[2]; Wafaie Fawzi[3]

[1]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [2]Management and Development for Health, Dar es Salaam, United Republic of Tanzania; [3]Harvard School of Public Health, Boston, MA, US; [4]Muhimbili University of Health and Allied Sciences, Dar es Salaam, United Republic of Tanzania

607 HIV Drug Resistance Surveillance in Honduras After 10 Years of Widespread ART

Claudia Garcia-Morales[1]; **Santiago Avila-Rios**[1]; Daniela Tapia-Trejo[1]; Rita Meza[2]; Sandra Nuñez-Rubio[2]; Norma Flores[5]; Wendy Murillo[3]; Ivette Lorenzana[3]; Elsa Palou[4]; Gustavo Reyes-Terán[1]

[1]National Institute of Respiratory Diseases, Mexico City, Mexico; [2]Honduran HIV National Program and National Laboratory, Tegucigalpa, Honduras; [3]Universidad Nacional Autónoma de Honduras, Tegucigalpa, Honduras; [4]Hospital Escuela Universitario, Tegucigalpa, Honduras; [5]Instituto Nacional Cardiopulmonar, Tegucigalpa, Honduras

608 High Prevalence of Genotypic Resistance to Integrase inhibitors of HIV-1 Strains in Taiwan

Sui-Yuan Chang[1]; Chien-Ching Hung[2]

[1]National Taiwan University, Taipei, Taiwan; [2]National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

609 Integrase Resistance Correlates of Response to Dolutegravir (DTG) Through 48 Weeks

Cindy L. Vavro; Jenny Huang; Mounir Ait-Khaled

GlaxoSmithKline, Research Triangle Park, NC, US

610 Discordant Predictions Could Impact Dolutegravir Use Upon Raltegravir Failure

Kristof Theys[1]; Ana B. Abecasis[2]; Pieter Libin[1]; Perpétua Gomes[2]; Joaquim Cabanas[3]; Ricardo J. Camacho[1]; Kristel Van Laethem[1]
the Portuguese HIV-1 Resistance Study Group

[1]University of Leuven, Leuven, Belgium; [2]Universidade Nova de Lisboa, Lisbon, Portugal; [3]Hospital Egas Moniz, Lisbon, Portugal

611 Integrase S119P Mutation Correlates With Disease Progression in HIV-1 Naïve Patients

Daniele Armenia[1]; Maria Mercedes Santoro[1]; Caterina Gori[2]; Emanuele Nicastri[2]; Antonio Cristaudo[3]; Massimo Andreoni[4]; Andrea Antinori[2]; Zeger Debyser[5]; Carlo-Federico Perno[2]; Francesca Ceccherini-Silberstein[1]

[1]University of Rome Tor Vergata, Rome, Italy; [2]L. Spallanzani Hospital, Rome, Italy; [3]San Gallicano Dermatological Institute, Rome, Italy; [4]University Hospital Tor Vergata, Rome, Italy; [5]Katholieke Universiteit Leuven, Leuven, Belgium

TUESDAY, FEBRUARY 24, 2015

Session P-M1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Nucleic-Acid–Based Detection of HIV

612 A Generalized Entropy Measure of Viral Diversity for Identifying Recent HIV-1 Infections

Julia W. Wu; Oscar Patterson-Lomba; Marcello Pagano

Harvard School of Public Health, Boston, MA, US

613 Acute Infections, Cost and Time to Reporting of HIV Test Results in US State Public Health Laboratories

Muazzam Nasrullah[1]; Laura G. Wesolowski[1]; Steven F. Ethridge[1]; Kevin Cranston[2]; Robert A. Myers[3]; James T. Rudrik[4]; Angela B. Hutchinson[1]; Barbara G. Werner[2]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]Massachusetts Department of Public Health, Boston, MA, US; [3]Maryland Department of Health and Mental Hygiene, Baltimore, MD, US; [4]Michigan Department of Community Health, Lansing, MI, US

614 The POC Alere q HIV-1/2 Detect Test for Detection and Quantification of HIV-2

Ming Chang[1]; Katja Weimar[2]; Dana N. Raugi[1]; Robert A. Smith[1]; Selly Ba[3]; Moussa Seydi[3]; Katrin Steinmetzer[2]; Robert W. Coombs[1]; **Geoffrey S. Gottlieb**[1]
UW-Dakar HIV-2 Study Group

[1]University of Washington, Seattle, WA, US; [2]Alere Technologies GmbH, Jena, Germany; [3]Service des Maladies Infectieuses, CHNU de Fann, Dakar, Senegal

615 Performance of HIV Viral Load with Dried Blood Spots in Children on ART in Mozambique

Amina M. de Sousa Muhate[1]; James C. Houston[2]; Mariamo Assane[1]; Joy Chang[2]; Emilia Koumans[2]; Ilesh V. Jani[1]; Jennifer Sabatier[2]; Paula M. Vaz[3]; Chunfu Yang[2]; Emilia Rivadeneira[2]

[1]Ministry of Health, Mozambique, Mozambique; [2]Centers for Disease Control and Prevention, Atlanta, GA, US; [3]Fundação Ariel Glaser Contra o SIDA Pediátrico, Maputo, Mozambique

616 Cost-Effectiveness of Pooled PCR Testing of Dried Blood Spots for Infant HIV Diagnosis

Cari van Schalkwyk[2]; Jean Maritz[2]; **Alex Welte**[1]; Gert U. van Zyl[2]; Wolfgang Preiser[2]

[1]University of Stellenbosch, South Africa, Stellenbosch, South Africa; [2]University of Stellenbosch, Tygerberg, South Africa

617 Evaluating Dried Blood Spot Performance in Assessing HIV Treatment Failure in Uganda

Allen Roberts; Herbert C. Duber; Ming Chang; Anne Gasasira; Gloria Ikilezi; Jane Achan; Joan Dragavon; Glenda Daza; Emmanuela Gakidou; Robert W. Coombs

Makerere University College of Health Sciences, Kampala, Uganda

618 Comparison of Pooled RNA and 4th Gen Ag/Ab Testing to Identify Acute HIV Infection

Gary Murphy; Simon Carne; Bharati Patel; Elaine Mckinney; Samual Moses; Noel Gill; John Parry; Jennifer Tosswill

Public Health England, London, United Kingdom

619 Improved Viral Load Monitoring Capacity With Rank-Based Algorithms for Pooled Assays

Tao Liu[1]; **Joseph Hogan**[1]; Renxia Huang[3]; Rami Kantor[2]

[1]Brown University, Providence, RI, US; [2]Miriam Hospital, Alpert Medical School, Brown University, Providence, RI, US; [3]Fulcrum Analytics Inc, Fairfield, CT, US

WEDNESDAY, FEBRUARY 25, 2015

Session P-M2 Poster Session **Poster Hall**
2:30 pm – 4:00 pm

Comparison of HIV Incidence Assays

620 Evaluation of Determine™ HIV-1/2 Ag/Ab Combo in the Context of Acute HIV Screening

Silvina Masciotra[1]; S. Michele Owen[1]; Wei Luo[1]; Emily Westheimer[2]; Stephanie Cohen[3]; Laura Hall[4]; Cindy L. Gay[5]; Philip J. Peters[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]New York City Department of Health and Mental Hygiene, New York, NY, US; [3]San Francisco Department of Public Health, San Francisco, CA, US; [4]ICF International, Atlanta, GA, US; [5]University of North Carolina, Chapel Hill, NC, US

621 Performance of the Geenius HIV-1/HIV-2 Assay in the CDC HIV Testing Algorithm

Kevin P. Delaney; Steven Ethridge; Laura G. Wesolowski; MIchele Owen; Bernard M. Branson

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

622 The Effect of HIV-1 Subtype A, C and D on Cross-Sectional Incidence Assay Performance

Andrew F. Longosz[2]; Mary Grabowski[2]; Charles S. Morrison[3]; Ronald H. Gray[2]; Connie Celum[4]; Quarraisha Abdool Karim[5]; Hilmarie Brand[6]; Thomas C. Quinn[1]; Susan H. Eshleman[2]; **Oliver B. Laeyendecker**[1]

[1]National Institute of Allergy and Infectious Diseases, Baltimore, MD, US; [2]Johns Hopkins University, Baltimore, MD, US; [3]FHI 360, Durham, NC, US; [4]University of Washington, Seattle, WA, US; [5]CAPRISA, University of KwaZulu-Natal, Congella, South Africa; [6]SACEMA, Stellenbosch University, Stellenbosch, South Africa

623 Avidity Assay for Cross-Sectional Incidence Based on a 4th-Generation Combo Ag/Ab EIA

Allison R. Kirkpatrick[1]; Eshan U. Patel[1]; Connie L. Celum[2]; Richard D. Moore[3]; Joel N. Blankson[3]; Shruti H. Mehta[4]; Gregory D. Kirk[4]; Thomas C. Quinn[1]; Susan H. Eshleman[2]; Oliver B. Laeyendecker[1]

[1]National Institutes of Health, Baltimore, MD, US; [2]University of Washington, Seattle, WA, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]Johns Hopkins University School of Medicine, Baltimore, MD, US

624 Estimation of HIV Incidence in a High-HIV-Prevalence Setting, South Nyanza, Kenya, 2012

Andrea A. Kim[1]; David Maman[2]; Harrison Fredrick Omondi[3]; Alex Morwabe[3]; Irene Mukui[4]; Valarie Opollo[3]; Beatrice Kirubi[5]; Jean-François Etard[2]; Martinus W. Borgdorff[7]; **Clement Zeh**[7]

[1]US Centers for Disease Control and Prevention, Dpo, AE, US; [2]Médecins Sans Frontières, Paris, France; [3]Kenya Medical Research Institute (KEMRI)/CDC Research and Public Health Collaboration, Kisumu, Kenya; [4]Kenya Ministry of Health, Nairobi, Kenya; [5]Médecins Sans Frontières, Nairobi, Kenya; [6]US Centers for Disease Control and Prevention (CDC), Kisumu, Kenya; [7]US Centers for Disease Control and Prevention (CDC), Kisumu, Kenya

625 False Recent Rates for Two Recent Infection Testing Algorithms, South Nyanza, Kenya

Clement Zeh[1]; David Maman[4]; Harrison Omondi[2]; Alex Morwabe[2]; Collins Odhiambo[2]; Beatrice Kirubi[4]; Irene Mukui[3]; Martinus W. Borgdorff[1]; Jean-François Etard[4]; Andrea A. Kim[1]

[1]US Centers for Disease Control and Prevention, Kisumu, Kenya; [2]Kenya Medical Research Institute, Kisumu, Kenya; [3]National AIDS and STI Control and Prevention, Nairobi, Kenya; [4]Médecins Sans Frontières, Paris, France

626 Viral Load is Critical in Limiting False-Recent Results From HIV Incidence Assays

Reshma Kassanjee[1]; Shelley Facente[2]; Sheila Keating[3]; Elaine McKinney[4]; Kara Marson[2]; Christopher D. Pilcher[2]; Michael Busch[3]; Gary Murphy[4]; **Alex Welte**[1]
The Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA)

[1]South African DST/NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), University of Stellenbosch, Stellenbosch, South Africa; [2]University of California San Francisco, San Francisco, CA, US; [3]Blood Systems Research Institute, San Francisco, CA, US; [4]Public Health England, London, United Kingdom

627 Use of the Sample-to-Cutoff Ratio (S/CO) to Identify Recency of HIV-1 Infection

Eric M. Ramos; José Ortega; Glenda Daza; Yuree Namkung; Socorro Harb; Joan Dragavon; Robert W. Coombs

University of Washington, Seattle, WA, US

628 An Abbott Architect Combo Signal to Cut-Off Ratio With Adequate PPV to Confirm HIV

Tomas O. Jensen[1]; Peter Robertson[2]; **Jeffrey J. Post**[1]

[1]Prince of Wales Hospital, Randwick, Australia; [2]South Eastern Area Laboratory Services, Prince of Wales Hospital, Sydney, Australia

629 Determining HIV Status of African Adults With Discordant HIV Rapid Tests

Jessica M. Fogel[1]; Estelle Piwowar-Manning[1]; Mark A. Marzinke[1]; William Clarke[1]; Michal Kulich[2]; Jessie K. Mbwambo[3]; Linda Richter[4]; Glenda Gray[5]; Thomas J. Coates[6]; Susan H. Eshleman[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Charles University, Prague, Czech Republic; [3]Muhimbili University Teaching Hospital, Dar es Salaam, United Republic of Tanzania; [4]Universities of the Witwatersrand and KwaZulu-Natal, Durban, South Africa; [5]South African Medical Research Council, Cape Town, South Africa; [6]David Geffen School of Medicine and University of California Los Angeles Health, Los Angeles, CA, US

Session P-M3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HIV Detection, Tropism, and CD4 Measurement

630 Accuracy of POC CD4 testing using microtube capillary sampling in Botswana households

Sikhulile Moyo[1]; Lillian Okui[1]; Hermann Bussmann[1]; Simani Gaseitsiwe[1]; Erik van Widenfeldt[1]; Molly P. Holme[2]; Joseph Makhema[1]; Shahin Lockman[2]; Vladimir Novitsky[2]; Max Essex[2]

[1]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana; [2]Harvard School of Public Health, Boston, MA, US

631 Zyomyx MyT4 and BD FACSPresto Comparison to the Pima CD4 Assay

Katie Tucker; Sehin Birhanu; Larry Westerman

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

632LB Point-of-Care CD4 (Pima) Impact on Linkage to Care With Home-Based HIV Testing, Kenya

Mitesh A. Desai[1]; Duncan Okal[2]; Robert T. Chen[1]; Richard Ndivo[2]; Charles Lebaron[1]; Tiffany Williams[1]; Fred Otieno[2]; Charles Rose[1]; Taraz Samandari[1]; Clement Zeh[1]

[1]US Centers for Disease Control and Prevention, Atlanta, GA, US; [2]Kenya Medical Research Institute, Kisumu, Kenya

633 Reliable Genotypic Tropism Tests for the Major HIV-1 Subtypes

Kieran Cashin[1]; Lachlan R. Gray[1]; Katherine L. Harvey[1]; Danielle Perez-Bercoff[2]; Guinevere Q. Lee[3]; Jasminka Sterjovski[1]; James F. Demarest[4]; Fraser Drummond[4]; Melissa J. Churchill[1]; Paul R. Gorry[1]

[1]Burnet Institute, Melbourne, Australia; [2]Centre Recherche Public de la Santé, Strassen, Luxembourg; [3]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; [4]ViiV Healthcare, Durham, NC, US

634 Accuracy of Re-Reading HIV Rapid Tests and the Effect of Prolonged High Temperature

Augustine T. Choko[1]; Deus Thindwa[1]; Peter MacPherson[2]; Rodrick Sambakunsi[1]; Aaron Mdolo[1]; Kondwani Chiumya[1]; Owen Malema[3]; Simon Makombe[4]; Emily L. Webb[6]; **Elizabeth L. Corbett**[6]

[1]Malawi Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi; [2]University of Liverpool, Liverpool, United Kingdom; [3]Ministry of Health, Blantyre, Malawi; [4]Ministry of Health, Lilongwe, Malawi; [5]London School of Hygiene and Tropical Medicine, London, United Kingdom; [6]London School of Hygiene and Tropical Medicine, London, United Kingdom

635 Analysis of False Negative HIV Tests Based on Oral Fluid in 3 Clinical Trials

Marcel E. Curlin[1]; Michael T. Martin[1]; Wanna Leelawiwat[2]; Roman Gvetadze[1]; Charles Rose[1]; Sarika Pattanasin[2]; Richard Niska[1]; Timothy Holtz[1]; Kachit Choopanya[3]; Janet McNicholl[1]

[1]US Centers for Disease Control and Prevention, Apo, US; [2]Thailand Ministry of Public Health–Centers for Disease Control and Prevention Collaboration, Nonthaburi, Thailand; [3]Bangkok Tenofovir Study Group, Bangkok, Thailand

TUESDAY, FEBRUARY 24, 2015

Session P-N1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Natural History and Prognosis of HCV Infection

636 Progression of Liver Disease in LHIV/HCV Coinfected People According to Gender in Icona Cohort: Role of Age as Potential Different Exposure to Estrogens

Antonella Cingolani[1]; Paola Cicconi[2]; Gloria Taliani[3]; Alessandro D. Cozzi-Lepri[4]; Massimo Puoti[5]; Carmela Pinnetti[6]; Pier Luigi Viale[7]; Antonella d'Arminio Monforte[2]
for Icona Foundation Study Group

[1]Catholic University, Roma, Italy; [2]University of Milano, Milano, Italy; [3]University La Sapienza, Roma, Italy; [4]University College London Medical School, Royal Free Campus, London, United Kingdom, London, United Kingdom; [5]Niguarda Hospital, Milano, Italy; [6]National Institute for Infectious Diseases L. Spallanzani, Roma, Italy; [7]Univeristy of Bologna, Bologna, Italy

637 A Prognostic Score Estimating the Risk of Liver-Related Death Among HIV/HCV Coinfected Subjects

Daniel Grint[1]; Lars Peters[2]; Jürgen Rockstroh[3]; Karine Lacombe[4]; Andrzej Horban[5]; Irina Khromova[8]; Jose Gatell[6]; Antonella d'Arminio Monforte[7]; Jens D. Lundgren[2]; **Amanda Mocroft**[1]
on behalf of EuroSIDA in EuroCoord

[1]University College London, London, United Kingdom; [2]University of Copenhagen, Copenhagen, Denmark; [3]University Hospital Bonn, Bonn, Germany; [4]Hospital Saint Antoine, Paris, France; [5]Wojewodzki Szpital Zakazny, Warsaw, Poland; [6]University of Barcelona, Barcelona, Spain; [7]Clinica delle Malattie Infettive e Tropicali, Milan, Italy; [8]Centre for HIV/AIDS & Infectious Diseases Prevention & Control, Kaliningrad, Russian Federation

638 Has Modern ART Reduced Endstage Liver Disease Risk in HIV-Hepatitis Coinfection?

Marina B. Klein[1]; Keri N. Althoff[3]; Yuezhou Jing[3]; Greg D. Kirk[3]; Vincent Lo Re[2]; Nina Kim[4]; Mari Kitahata[4]; Chloe Thio[3]; Michael J. Silverberg[5]; Richard Moore[3]
North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)

[1]McGill University Health Centre, Montreal, Canada; [2]University of Pennsylvania, Philadelphia, PA, US; [3]Johns Hopkins University, Baltimore, MD, US; [4]University of Washington, Washington, DC, US; [5]Kaiser Permanente Northern California, Oakland, CA, US

639 Marijuana Use Does Not Accelerate Liver Fibrosis in HCV/HIV-Coinfected Women

Erin M. Kelly[1]; Jennifer L. Dodge[1]; Monika Sarkar[1]; Audrey French[2]; Phyllis Tien[1]; Marshall Glesby[3]; Elizabeth Golub[4]; Michael Augenbraun[5]; Michael Plankey[6]; **Marion G. Peters**[1]
WIHS

[1]University of California San Francisco, San Francisco, CA, US; [2]CORE Center/Stroger Hospital, Chicago, IL, US; [3]Weill Cornell Medical College, New York City, NY, US; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]State University of New York, Downstate Medical Center, Brooklyn, NY, US; [6]Georgetown University, Washington, DC, US

640 HIV Infection Does Not Worsen Prognosis of Liver Transplantation for Hepatocellular Carcinoma

Fernando H. Agüero[1]; Alejandro Forner[2]; Christian Manzardo[1]; Andres Valdivieso[3]; Marino Blanes[4]; Rafael Barcena[5]; Antoni Rafecas[1]; Lluis Castells[6]; Antonio Rimola[1]; Jose M Miro[1]

[1]University of Barcelona, Barcelona, Barcelona, Spain; [2]Hospital Clinic, IDIBAPS and El Centro de Investigación Biomédica en Red en el Área Temática de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; [3]Hospital Universitario de Cruces, Bilbao, Spain, Bilbao, Spain; [4]Hospital Universitario La Fe, Valencia, Spain, Valencia, Spain; [5]Hospital Universitario Ramón y Cajal, Madrid, Spain, Madrid, Spain; [6]Hospital Universitari Vall d'Hebrón, Barcelona, Spain, Barcelona, Spain

641 Rapid Progression to Cirrhosis and Death Among HCV-Infected Persons Who Inject Drugs in India

Shruti H. Mehta[1]; Suniti Solomon[2]; Allison M. McFall[1]; Aylur K. Srikrishnan[2]; Pachamuthu Balakrishnan[2]; Nandagopal P[2]; David L. Thomas[1]; Mark Sulkowski[1]; Sunil S. Solomon[1]

[1]Johns Hopkins University, Baltimore, MD, US; [2]YR Gaitonde Centre for AIDS Research and Education, Chennai, India

642 Chronic Kidney Disease Progression After HCV Seroconversion

Adeel A. Butt

University of Pittsburgh/VA Pittsburgh Healthcare System, Pittsburgh, PA, US

Session P-N2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HCV Therapy: Observations From Cohort Studies

643 Statins Improve SVR, Reduce Fibrosis Progression and HCC Among HCV+ Persons

Adeel A. Butt[1]; Peng Yan[2]; Obaid Shaikh[2]; Shari Rogal[2]

[1]University of Pittsburgh/VA Pittsburgh Healthcare System, Pittsburgh, PA, US; [2]VA Pittsburgh Healthcare System, Pittsburgh, PA, US

644 Sofosubuvir, Simeprevir, +/- Ribavirin in HCV Protease Inhibitor-Experienced Patients

Kristen M. Marks; Ethan M. Weinberg; Sonal Kumar; Carrie Down; Ype P. de Jong; Leah A. Burke; Mary C. Olson; Ira M. Jacobson

Weill Cornell Medical College, New York, NY, US

645 Effectiveness of Sofosbuvir/Simeprevir for HIV/HCV Patients in Clinical Practice

Jody Gilmore[1]; Kenneth Lynn[1]; Delisha Breen[1]; Stacey Trooskin[2]; Jihad Slim[3]; Nancy Scangarello[3]; Alvin Kingcade[4]; Katie Hunyh[4]; Vincent Lo Re[1]; **Jay R. Kostman**[1]

[1]Perelman School of Medicine, Philadelphia, PA, US; [2]Drexel University College of Medicine, Philadelphia, PA, US; [3]St Michael's Medical Center, Newark, NJ, US; [4]Philadelphia Health Management Corporation, Philadelphia, PA, US

646 German Cohort on Sofosbuvir-Based Therapy for HIV/HCV and HCV Infection (GECOSO)

Stefan Christensen[2]; Ingiliz Patrick[3]; Dietrich Hueppe[7]; Thomas Lutz[4]; Karl Georg Simon[6]; Knud Schewe[5]; Heiner Busch[2]; Axel Baumgarten[3]; Guenther Schmutz[1]; **Stefan Mauss**[1]

[1]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; [2]CIM Infectious Diseases, Muenster, Germany; [3]Medizinisches Infektiologie Zentrum Berlin, Berlin, Germany; [4]Infektiologikum, Frankfurt, Germany; [5]Infektionsmedizinisches Centrum Hamburg, Hamburg, Germany; [6]Practice for Gastroenterology Leverkusen, Leverkusen, Germany; [7]Practice for Gastroenterology Herne, Herne, Germany

647 Real-World Data on HIV-Positive Patients With HCV Treated With Sofosbuvir and/or Simeprevir

David Del Bello[1]; Kian Bichoupan[1]; Calley Levine[1]; Agnes Cha[2]; David Perlman[1]; Nadim H. Salomon[1]; Donald Kotler[1]; Daniel Fierer[1]; Douglas Dieterich[1]; Andrea Branch[1]

[1]Mount Sinai Health System, New York City, NY, US; [2]Brooklyn Medical Center, New York City, NY, US

648 Simeprevir and Sofosbuvir Regimens for Hepatitis C: Decompensation and Serious AEs

Ponni V. Perumalswami[1]; Kian Bichoupan[1]; Lawrence Ku[1]; Neal M. Patel[1]; Rachana Yalamanchili[1]; Thomas Schiano[1]; Mark Woodward[2]; Douglas Dieterich[1]; Andrea D. Branch[1]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, US; [2]George Institute for Health at the University of Oxford, Oxford, United Kingdom

649 Successful HCV Treatment With Direct Acting Antivirals in HIV/HCV Patients

Jennifer L. Grant[1]; Valentina Stosor[1]; Frank J. Palella[1]; Richard M. Green[1]; Guajira Thomas[1]; Donna V. McGregor[1]; Milena M. McLaughlin[2]; Sudhir Penugonda[1]; Michael Angarone[1]; **Claudia Hawkins**[1]

[1]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [2]Midwestern University, Chicago, IL, US

650 Sofosbuvir/Daclatasvir in HIV/HCV Co-infected Patients With Extensive Liver Fibrosis

Alissa Naqvi; Francine Guillouet de Salvador; Isabelle Perbost; Brigitte Dunais; Aline Joulié; Rodolphe Garraffo; Pascal Pugliese; Jacques Durant; Pierre Marie Roger; Eric Rosenthal

Centre Hospitalier Universitaire de Nice, Nice, France

651 Majority of HIV/HCV Patients Need to Switch ART to Accommodate Simeprevir

Rebecca Cope[1]; Aaron Pickering[2]; Thomas Glowa[1]; Samantha Faulds[1]; Peter Veldkamp[1]; **Ramakrishna Prasad**[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]University of Maryland, Glen Burnie, MD, US

Session P-N3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Treatment of HCV with DAAs: Short-Term Costs and Long-Term Benefits

652 Simeprevir/Sofosbuvir vs Triple Therapy (Telaprevir or Boceprevir) for HCV GT1: A cost analysis

Jacob A. Langness[1]; David Tabano[2]; Sarah Tise[3]; Lindsay Pratt[3]; Lauren Ayres[3]; Amanda Wieland[3]; Sonia Lin[1]; Vahram Ghuschcyan[2]; Kavita Nair[2]; Greg Everson[3]

[1]University of Colorado, Arvada, CO, US; [2]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Aurora, CO, US; [3]University of Colorado, Aurora, CO, US

653 SVR Durability: HCV Patients Treated With IFN-Free DAA Regimens

Aurielle M. Thomas[1]; Sarah Kattakuzhy[1]; Sarah Jones[2]; Anita Kohli[1]; Wilson Eleanor[2]; Angie Price[2]; Rachel Silk[2]; Zayani Sims[1]; Anu Osinusi[3]; Shyam Kottilil[3]

[1]The National Institutes of Health, Bethesda, MD, US; [2]Leidos Biomedical Research, Inc., Bethesda, MD, US; [3]Institute of Human Virology, University of Maryland, Baltimore, MD, US

654 Five–Year Risk of Late Relapse or Reinfection With Hepatitis C After Sustained Virological Response: Meta-analysis of 49 Studies in 8534 Patients

Andrew M. Hill[1]; Bryony Simmons[2]; Jawaad Saleem[2]; Graham Cooke[2]

[1]Chelsea and Westminster Hospital, London, United Kingdom; [2]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom

655 Incidence of Extrahepatic Complications in HIV/HCV Patients Who Achieved SVR

Sebastiano Leone[1]; Mattia Prosperi[2]; Silvia Costarelli[1]; Francesco Castelli[3]; Franco Maggiolo[4]; Simona Di Giambenedetto[5]; Annalisa Saracino[6]; Massimo Di Pietro[7]; Fabio Zacchi[8]; Andrea Gori[1]

[1]"San Gerardo Hospital", University of Milano-Bicocca, Monza, Italy; [2]University of Manchester, Manchester, United Kingdom; [3]University of Brescia, Brescia, Italy; [4]Ospedali Riuniti, Bergamo, Italy; [5]Policlinico Gemelli, Rome, Italy; [6]Policlinico of Bari, Bari, Italy; [7]S.M Annunziata Hospital, Firenze, Italy; [8]Istituti Ospeitalieri di Cremona, Cremona, Italy

656 Impact of SVR on Liver Decompensation and Hepatic Fibrosis Markers in HIV/HCV

Janet Tate[1]; E. John Wherry[2]; Jay R. Kostman[2]; Debika Bhattacharya[4]; Guadalupe Garcia-Tsao[5]; Cynthia Gibert[6]; Joseph K. Lim[5]; David Rimland[3]; Amy Justice[1]; **Vincent Lo Re**[2]
Veterans Aging Cohort Study Project Team

[1]VA Connecticute Health System, West Haven, CT, US; [2]Univeristy of Pennsylvania, Philadelphia, PA, US; [3]Atlanta VA Healthcare System, Atlanta, GA, US; [4]VA Greater Los Angeles, Los Angeles, CA, US; [5]Yale University School of Medicine, New Haven, CT, US; [6]Washington DC VA Medical Center, Washington, DC, US

657 Portal Pressure Changes After HCV Eradication in HIV/HCV+ Patients With Cirrhosis

Matilde Sánchez-Conde; Leire Pérez-Latorre; Diego Rincón; Pilar Miralles; María Vega Catalina; Juan Carlos López; Rafael Bañares; **Juan Berenguer**

Hospital General Universitario Gregorio Marañón, Madrid, Spain

Session P-N4 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HCV: Getting the Drugs to Those Who Need Them

658 Assessment of PCP Knowledge of HCV Screening, Recommendations, and Treatment Options

Allison Brodsky; Monique Allen; Gregory Johnson; Lora Magaldi; Carolyn Moy; Nancy Tursi; Stephanie Tzarnas; Stacey Trooskin

Drexel University College of Medicine, Philadelphia, PA, US

659 Majority of HCV/HIV-Infected Patients in the Netherlands Remain in Need of Effective HCV Treatment

Colette Smit[1]; Joop E. Arends[2]; Marc van der Valk[3]; Kees Brinkman[4]; Heidi Ammerlaan[5]; S. Arend[6]; Peter Reiss[1]; Clemens Richter[7]

[1]Stichting HIV Monitoring, Amsterdam, Netherlands; [2]Universitair Medisch Centrum Utrecht, Utrecht, Netherlands; [3]Academic Medical Center, Amsterdam, Netherlands; [4]Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands; [5]CZE, Eindhoven, Netherlands; [6]Leiden University Medical Center, Leiden, Netherlands; [7]Rijnstate Ziekenhuis, Arnhem, Netherlands

660 Identifying and Prioritizing Hepatitis C Treatment for HIV-Hepatitis C Co-Infection

Amanda D. Castel[1]; Mariah M. Kalmin[1]; Rachel Hart[2]; Alan Greenberg[1]; Henry Masur[3]
DC Cohort Executive Committee

[1]The Milken Institute School of Public Health at George Washington University, Washington, DC, US; [2]Cerner Corporation, Kansas City, MO, US; [3]National Institutes of Health (NIH), Bethesda, MD, US

661 One-Year Results of a Community-Based Hepatitis C Testing and Linkage-to-Care Program

Christian B. Ramers[1]; Robert Lewis[1]; Letty Reyes[1]; Danelle Wallace[1]; Robert Gish[3]; David Wyles[2]; Alex Kuo[1]

[1]Family Health Centers of San Diego, San Diego, CA, US; [2]University of California San Diego, La Jolla, CA, US; [3]Stanford University, Palo Alto, CA, US

WEDNESDAY, FEBRUARY 25, 2015

Session P-N5 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HCV: Epidemiology and Case Detection

662 Hepatitis C and B Testing Among HIV-Infected Individuals in England

Sam Lattimore; Sarah Collins; Celia Penman; Lukasz Cieply; Sema Mandal
Sentinel Surveillance of Blood-Borne Virus Testing
Public Health England, London, United Kingdom

663 WITHDRAWN

664 HCV 2k/1b Recombinant Form among Hepatitis C–Infected Genotype 2 Patients in Georgia

Marika Karchava[1]; Jesper Waldenstrom[2]; Monica M. Parker[3]; Renee Hallack[3]; Lali Sharvadze[1]; Lana Gatserelia[1]; Nikoloz Chkhartishvili[1]; Natia Dvali[1]; Helen Norder[2]; Tengiz Tsertsvadze[1]

[1]Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi, Georgia; [2]Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden; [3]Wadsworth Center, Albany, NY, US

665 High HCV Prevalence Among Baby Boomers in Surveillance-Identified High HIV Risk Areas

Irene Kuo[1]; Meriam Mikre[1]; A. Toni Young[2]; Geoffrey Maugham[2]; Amanda D. Castel[1]

[1]George Washington University, Washington, DC, US; [2]Community Education Group, Washington, DC, US

666 Low HCV Screening Uptake of the Current Birth Cohort Testing Guidelines

Alexander G. Geboy[1]; Hyun A. Cha[1]; Idene E. Perez[1]; Matthew T. Bell[1]; Sandeep Mahajan[2]; Adebisi O. Ayodele[2]; Dawn A. Fishbein[2]

[1]MedStar Health Research Institute, Hyattsville, MD, US; [2]MedStar Washington Hospital Center, Washington, DC, US

667 Evaluation of CDC Recommendations for HCV Testing in an Urban Emergency Department

Yu-Hsiang Hsieh[3]; Richard Rothman[3]; Oliver B. Laeyendecker[2]; Gabor Kelen[3]; Ama Avornu[3]; Eshan U. Patel[2]; Jim Kim[3]; Risha Irvin[3]; David L. Thomas[3]; Thomas C. Quinn[2]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]National Institute of Allergy and Infectious Diseases, Baltimore, MD, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US

668 Impact of Integrating EMR HCV Testing Prompts in a Difficult to Navigate EMR System

Stephanie Tzarnas[2]; Monique Allen[2]; Allison Brodsky[2]; Gregory Johnson[2]; Lora Magaldi[2]; Carolyn Moy[2]; Nancy Tursi[2]; Steven Zivich[2]; Stacey Trooskin[2]

[1]Drexel University College of Medicine, Philadelphia, PA, US; [2]Drexel University College of Medicine, Philadelphia, PA, US; [3]Drexel University College of Medicine, Philadelphia, PA, US; [4]Drexel University College of Medicine, Philadelphia, PA, US

Session P-N6 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Acute HCV Infection

669 SVR12 Results After 12w Boceprevir + P/R in the Dutch Acute Hepatitis C in HIV Study

Sebastiaan J. Hullegie[8]; Mark A. Claassen[8]; Guido E. van den Berk[2]; Jan T. van der Meer[1]; Joop E. Arends[3]; Clemens Richter[4]; Dirk Posthouwer[5]; Peter P. Koopmans[6]; Fanny N. Lauw[7]; Bart J. Rijnders[8]

[1]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [2]Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands; [3]University Medical Center Utrecht, Utrecht, Netherlands; [4]Rijnstate Ziekenhuis, Arnhem, Netherlands; [5]Maastricht University Medical Center, Maastricht, Netherlands; [6]Radboud University Medical Center, Nijmegen, Netherlands; [7]Slotervaart Ziekenhuis, Amsterdam, Netherlands; [8]Erasmus University Medical Center, Rotterdam, Netherlands

670 Does the Availability of New DAAs Influence Treatment Uptake in Acute Hepatitis C in HIV Coinfection?

Christoph Boesecke[1]; Mark Nelson[2]; Patrick Ingiliz[5]; Thomas Lutz[3]; Stefan H. Scholten[4]; Christoph D. Spinner[6]; Michael Rausch[9]; Thomas Reiberger[7]; Stefan Mauss[8]; Jürgen Rockstroh[1]

[1]Bonn University Hospital, Bonn, Germany; [2]Chelsea and Westminster Hospital, NHS Foundation Trust, London, United Kingdom; [3]Infektiologikum, Frankfurt/Main, Germany; [4]Praxis Hohenstaufenring, Cologne, Germany; [5]MiB, Berlin, Germany; [6]Interdisciplinary HIV Centre (IZAR), University Hospital Klinikum Rechts der Isar, Munich, Germany; [7]Medical University of Vienna, Vienna, Austria; [8]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; [9]Aerztezentrum Nollendorfplatz, Berlin, Germany

671 Long-Term Follow-Up of HIV-Positive Men Who Have Sex With Men (MSM) With Acute Hepatitis C Virus (HCV) Infection: High Rates of Treatment and Low Rates of Liver-Related Complications

Patrick Ingiliz[1]; Anders C. Boyd[3]; Katharina Steininger[1]; Andreas Carganico[1]; Stephan Dupke[1]; Ivanka Krznaric[1]; Marcel Schuetze[1]; Stefan Neifer[2]; Martin J. Obermeier[1]; Axel Baumgarten[1]

[1]Medical Center for Infectious Diseases, Berlin, Germany; [2]Microbiology Laboratory, Berlin, Germany; [3]INSERM UMR_S 1136, Paris, France

672 Hepatitis C in Men Who Have Sex with Men With New HIV Diagnoses in Los Angeles

Kara W. Chew[1]; Marjan Javanbakht[2]; Laurel Clare[1]; Lorelei Bornfleth[1]; Debika Bhattacharya[1]; Pamina Gorbach[2]; Martha L. Blum[3]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, US; [2]UCLA Fielding School of Public Health, Los Angeles, CA, US; [3]Community Hospital of the Monterey Peninsula, Monterey, CA, US

673 Development and Comparison of Hepatitis C Cross-Sectional Incidence Testing Methods

Eshan U. Patel[1]; Andrea Cox[2]; Shruti H. Mehta[3]; Caroline E. Mullis[2]; Jeffrey Quinn[2]; Gregory D. Kirk[3]; Thomas C. Quinn[1]; Oliver B. Laeyendecker[1]

[1]National Institute of Allergy and Infectious Diseases (NIAID), Baltimore, MD, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

674 Risk Factors for Transmission of HCV Among HIV-Infected MSM: A Case-Control Study

Joost W. Vanhommerig[1]; Femke A. Lambers[1]; Janke Schinkel[2]; Joop E. Arends[3]; Fanny N. Lauw[4]; Kees Brinkman[5]; Luuk Gras[6]; Bart J. Rijnders[7]; Jan T. van der Meer[2]; Maria Prins[1]

[1]GGD Amsterdam, Amsterdam, Netherlands; [2]Academic Medical Center, Amsterdam, Netherlands; [3]University Medical Center Utrecht, Utrecht, Netherlands; [4]Slotervaart Hospital, Amsterdam, Netherlands; [5]OLVG Hospital, Amsterdam, Netherlands; [6]Dutch HIV Monitoring Foundation, Amsterdam, Netherlands; [7]Erasmus University Medical Center, Rotterdam, Netherlands; [8]Academic Medical Center, Amsterdam, Netherlands

675 Behavioural and Treatment Interventions to Reduce HCV Transmissions in HIV+ MSM

Luisa Salazar-Vizcaya[1]; Roger Kouyos[2]; Cindy Zahnd[1]; Manuel Battegay[3]; Katharine Darling[4]; Alexandra Calmy[5]; Pietro L. Vernazza[6]; Olivia Keiser[1]; Andri Rauch[7]
On behalf of the Swiss HIV Cohort Study

[1]University of Bern, Bern, Switzerland; [2]University Hospital Zurich, Zürich, Switzerland; [3]University Hospital Basel, Basel, Switzerland; [4]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [5]Geneva University Hospitals, Geneva, Switzerland; [6]Kantonsspital St Gallen, St Gallen, Switzerland; [7]University Hospital Bern, Inselspital, Bern, Switzerland

Session P-N7 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Immunopathogenesis of HCV Infection

676 Macrophage Activation and Hepatitis C (HCV) Disease Progression in HIV-Infected Women Participating in the Women's Interagency HIV Study (WIHS)

Audrey L. French[1]; Charlesnika Evans[3]; Marion G. Peters[2]; Mary A. Young[4]; Mark Kuniholm[6]; Michael Augenbraun[7]; Seema N. Desai[5]

[1]CORE Center/ Stroger Hospital of Cook County, Chicago, IL, US; [2]University of California San Francisco, San Francisco, CA, US; [3]Northwestern University, Chicago, IL, US; [4]Georgetown University, Washington, IL, US; [5]Rush University Medical Center, Chicago, IL, US; [6]Montefiore Medical Center, University Hospital for Albert Einstein College of Medicine, Bronx, NY, US; [7]State University of New York Downstate, Brooklyn, NY, US

677 HIV/HCV Co-Infection Accelerated Liver Disease is Associated With Induction of M2-Like Macrophages

Moses T. Bility[1]; Feng Li[1]; Junichi Nunoya[1]; Guangming Li[1]; Eoin Feeney[2]; Raymond Chung[2]; Lishan Su[1]

[1]University of North Carolina, Chapel Hill, NC, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

678 HIV Infection Is Associated With an Impaired Anti-HCV Activity of NK-Like T Cells

Pavlos Kokordelis[1]; Benjamin Krämer[1]; Christoph Boesecke[1]; Esther Voigt[2]; Patrick Ingiliz[3]; Andreas Glässner[1]; Franziska Wolter[1]; Ulrich Spengler[1]; Jürgen K. Rockstroh[1]; Jacob Nattermann[1]

[1]University of Bonn, Bonn, Germany; [2]Praxis am Ebertplatz, Cologne, Germany; [3]Medical Center for Infectious Diseases, Berlin, Germany

679 Dys-Regulated Cross Talk Between CD4+ T Cells and NK Cells in HIV/HCV Coinfection

Benjamin Krämer[1]; Andreas Glässner[1]; Claudia Zwank[1]; Felix Goeser[1]; Christoph Boesecke[1]; Patrick Ingiliz[2]; Christian P. Strassburg[1]; Ulrich Spengler[1]; Jürgen Rockstroh[1]; Jacob Nattermann[1]

[1]University of Bonn, Bonn, Germany; [2]Medical Center for Infectious Diseases, Berlin, Germany

680 HIV/HCV Coinfection Is Associated With Significant Alterations of the NK Cell Pool

Dominik J. Kaczmarek[1]; Pavlos Kokordelis[1]; Benjamin Krämer[1]; Andreas Glässner[1]; Franziska Wolter[1]; Patrick Ingiliz[2]; Christian P. Strassburg[1]; Ulrich Spengler[1]; Jürgen Rockstroh[1]; Jacob Nattermann[1]

[1]University of Bonn, Bonn, Germany; [2]Medical Center for Infectious Diseases, Berlin, Germany

681 Dynamic Changes of CXCL10 Isoforms and DPP4 During IFN-Free Treatment for HCV

Eric G. Meissner[1]; Jeremie Decalf[2]; Armanda Casrouge[2]; Henry Masur[3]; Shyam Kottilil[4]; Darragh Duffy[2]; Matthew L. Albert[2]

[1]Medical University of South Carolina, Charleston, SC, US; [2]Institut Pasteur, Paris, France; [3]National Institutes of Health (NIH), Bethesda, MD, US; [4]University of Maryland School of Medicine, Baltimore, MD, US

682 Mx1 and OAS1-2 SNPs Are Related With Severity of Liver Disease in HIV/HCV Coinfection

Mónica García-Álvarez[1]; Juan Berenguer[2]; Daniel Pineda-Tenor[1]; Maria Ángeles Jiménez-Sousa[1]; María Guzmán-Fulgencio[1]; Ana Carrero[2]; Teresa Aldamiz-Echevarria[2]; Francisco Tejerina[2]; Cristina Diez[2]; Salvador Resino[1]

[1]Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain; [2]Hospital General Universitario Gregorio Marañón, Madrid, Spain

683 Treatment With DCV Plus ASV Reduces Immune Activation in HIV/HCV Coinfected Patients

Eleanor M. Wilson[4]; Anita Kohli[3]; Julia B. Purdy[3]; Louisa Howard[1]; Sabrina Mangat[1]; Gebeyehu Teferi[2]; John Hogan[2]; Henry Masur[3]; Shyam Kottilil[1]

[1]National Institutes of Health (NIH), Bethesda, MD, US; [2]Unity Health Care, Washington, DC, US; [3]NIH, Bethesda, MD, US; [4]Leidos Biomedical Services, Inc, Bethesda, MD, US

684 Innate Immune Activation Pathways Overlap, Yet Are Distinct in HCV and HIV Infection

Lenche Kostadinova; Benigno Rodriguez; Donald Anthony

Case Western Reserve University, Cleveland, OH, US

685 A Novel Mechanism of Resistance to Multiple bNAbs Revealed by Natural Variation in Panel of 199 HCVpp

Ramy El-Diwany; Lisa Wasilewski; Madeleine Mankowski; Stuart C. Ray; Justin R. Bailey

Johns Hopkins University School of Medicine, Baltimore, MD, US

686 Single-Variant Sequencing Revealed Rapid HCV Evolution in HIV Immune Reconstitution

Lin Liu; David Nardo; Eric Li; Gary Wang

University of Florida, Gainesville, FL, US

THURSDAY, FEBRUARY 26, 2015

Session P-N8 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HCV Therapeutics: Preclinical Observations and Clinical Trials of DAAs

687 UNITY-1: Daclatasvir/Asunaprevir/Beclabuvir for HCV Genotype 1 Without Cirrhosis

Fred Poordad[1], William Sievert[2], Norbert Brau[3], **Samuel Lee**[4], Jean-Pierre Bronowicki[5], Ira Jacobson[6], Eric Hughes[7], Eugene Swenson[8], Philip Yin[8]
On behalf of the UNITY-1 Study Team

[1]Texas Liver Institute, San Antonio, Texas, United States; [2]Monash Health and Monash University, Melbourne, Victoria, Australia; [3]Bronx Veterans Affairs Medical Center, New York, New York, United States; [4]University of Calgary, Alberta Health Services, Calgary, Alberta, Canada; [5]Centre Hospitalier Universitaire de Nancy, Universite de Lorraine, Vandoeuvre les Nancy, France; [6]Weill Cornell Medical College, New York, New York, United States; [7]Bristol-Myers Squibb Co, Princeton, New Jersey, United States; [8]Bristol-Myers Squibb Co, Wallingford, Connecticut, United States

688 UNITY-2: Daclatasvir/Asunaprevir/Beclabuvir ± RBV for HCV Genotype 1 With Cirrhosis

Andrew Muir[1], Fred Poordad[2], Jay Lalezari[3], Gregory Dore[4], Christophe Hezode[5], Alnoor Ramji[6], Eric Hughes[7], **Eugene Swenson**[8], Philip Yin[88]
On behalf of the UNITY-2 Study Team

[1]Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina, United States; [2]Texas Liver Institute, University of Texas Health Science, San Antonio, Texas, United States; [3]Quest Clinical Research, San Francisco, California, United States; [4]Kirby Institute, University of New South Wales Australia, Sydney, New South Wales, Australia; [5]Hópital Henri Mondor, Université Paris-Est, Créteil, France; [6]University of British Columbia, Vancouver, British Columbia, Canada; [7]Bristol-Myers Squibb Co, Princeton, New Jersey, United States; [8]Bristol-Myers Squibb Co, Wallingford, Connecticut, United States

689 Utility of Hepatitis C Viral-Load Monitoring With Ledipasvir and Sofosbuvir Therapy

Sreetha Sidharthan[2]; Anita Kohli[3]; Anu Osinusi[2]; Amy Nelson[1]; Zayani Sims[2]; Kerry S. Townsend[4]; Lydia Tang[1]; Michael Polis[4]; Henry Masur[2]; Shyam Kottilil[1]

[1]Institute of Human Virology, University of Maryland, Baltimore, MD, US; [2]NIH Clinical Center, Bethesda, MD, US; [3]Leidos Biomedical Research, Inc., Frederick, MD, US; [4]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

690 Viral Kinetic Profiles of HCV Response to Telaprevir-Based Therapy in Patients With Hemophilia

Kenneth E. Sherman[1]; Ruian Ke[2]; Susan D. Rouster[1]; Alan S. Perelson[2]

[1]University of Cincinnati, Cincinnati, OH, US; [2]Los Alamos National Laboratory, Los Alamos, NM, US

691 Hematologic Analysis of ABT-450/r/Ombitasvir and Dasabuvir + RBV in TURQUOISE-I

Robert S. Brown[1]; David Wyles[2]; Jihad Slim[3]; Peter J. Ruane[4]; Barbara McGovern[5]; Roger Trinh[5]; Yiran Hu[5]; Joseph J. Eron[6]

[1]Johns Hopkins University, Baltimore, MD, US; [2]University of California San Diego, La Jolla, CA, US; [3]St Michael's Medical Center, Newark, NJ, US; [4]Peter J. Ruane MD Inc, Los Angeles, CA, US; [5]AbbVie, Inc, North Chicago, IL, US; [6]University of North Carolina, Chapel Hill, NC, US

692 Effect of HIV Coinfection on Adherence to a 12-Week Regimen of HCV Therapy With Ledipasvir/Sofosbuvir

Kerry S. Townsend[1]; Tess L. Petersen[2]; Lori A. Gordon[2]; Amy Nelson[1]; Cassie Seamon[2]; Chloe Gross[3]; Anu Osinusi[2]; Michael A. Polis[1]; Henry Masur[2]; Shyam Kottilil[1]

[1]National Institute of Allergy and Infectious Diseases, Bethesda, MD, US; [2]National Institutes of Health, Bethesda, MD, US; [3]Leidos Biomedical 18 Research Inc, Frederick, MD, US

693 Investigation of the Role of Macrocyclization in HCV Protease Inhibitor MK-5172

Djadé I. Soumana; Kristina Prachanronarong; Nese Kurt Yilmaz; Ali Akbar; Cihan Aydin; Celia A. Schiffer

University of Massachusetts Medical School, Worcester, MA, US

Session P-N9 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Mental Health and Treatment Adherence with Direct-Acting Antivirals

694 Impact of Baseline Mental Health on Adherence to Interferon-Free HCV Therapy

Jack Masur[1]; Lydia Tang[1]; Amy Nelson[1]; Anu Osinusi[1]; Anita Kohli[2]; Rachel Silk[2]; Chloe Gross[2]; Sarah Kattakuzhy[2]; Michael Polis[3]; Shyam Kottilil[1]

[1]University of Maryland, Baltimore, MD, US; [2]National Institutes of Health, Bethesda, MD, US; [3]National Institutes of Health, Bethesda, MD, US

695 Mental Health Impact of HCV Treatment in HIV/HCV Patients: DAA vs IFN-Based Therapy

Louise Lundgren[1]; Sarah Kattakuzhy[2]; Angie Price[2]; Catherine Seamon[3]; Amy Nelson[4]; Anita Kohli[2]; Rachel Silk[2]; Chloe Gross[2]; Henry Masur[1]; Shyamasundaran Kottilil[4]

[1]National Institutes of Health Clinical Center, Bethesda, MD, US; [2]Leidos Biomedical Research, Inc, Frederick, MD, US; [3]Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, US; [4]Institute of Human Virology, University of Maryland, Baltimore, MD, US

Session P-N10 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HCV: Resistance to Antiviral Agents

696 Characterization of Naturally Occurring Resistance to HCV NS5A Inhibitors

Jennifer Cook; Owen Solberg; Alicia Newton; Suqin Cai; Arne Frantzell; Jacqueline Reeves; Christos J Petropoulos; Jonathan Toma; **Wei Huang**

Monogram Biosciences, South San Francisco, CA, US

697 Hepatitis C Q80K Prevalence in BC, Canada, Determined by a Public Domain Assay

Jeffrey B. Joy[1]; Celia K. Chui[1]; Chanson J. Brumme[1]; Mel Krajden[2]; Andrea Olmstead[2]; Winnie Dong[1]; Wendy Zhang[1]; Aram Karakas[1]; Huong Hew[3]; Richard Harrigan[1]

[1]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; [2]BC Centre for Disease Control, Vancouver, Canada; [3]Janssen Pharmaceuticals, Inc., Toronto, Canada

698 HCVNS3 Variants in HIV/HCV Coinfected Patients Before-After PegIFN/Ribavirin

Enass Abdel-Hameed[1]; Susan D. Rouster[1]; Xiang Zhang[2]; Jing Chen[2]; Mario Medvedovic[2]; Kenneth E. Sherman[1]

[1]University of Cincinnati, Cincinnati, OH, US; [2]University of Cincinnati, Cincinnati, OH, US

699 Compensatory Mutations in HCV NS5A/B Coevolve in Patients Failing NS3 Inhibitors

Velia Chiara Di Maio[1]; Valeria Cento[1]; Daniele Di Paolo[2]; Sergio Babudieri[3]; Gloria Taliani[4]; Giustino Parruti[5]; Giuliano Rizzardini[6]; Mario Angelico[2]; Carlo Federico Perno[1]; **Francesca Ceccherini-Silberstein**[1]

[1]University of Rome Tor Vergata, Rome, Italy; [2]University Hospital of Rome Tor Vergata, Rome, Italy; [3]University of Sassari, Sassari, Italy; [4]University of Rome La Sapienza, Rome, Italy; [5]Pescara General Hospital, Pescara, Italy; [6]Hospital Sacco of Milan, Milan, Italy

Session P-N11 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Other Hepatitis Viruses: HBV, HDV, HEV

700 Hepatitis B Vaccine Response in Children Attending Rwanda Military Hospital

Judy T. Orikiiriza[1]; Louis Mujuwisha[2]; Elizabeth Karlsson[3]; Vincent Mutabazi[4]; Johan Normark[3]

[1]Infectious Diseases Institute Makerere College of Health Sciences, Kampala, Uganda; [2]University of Rwanda, Kigali, Rwanda; [3]Umea Infectious Diseases Institute, Kigali, Sweden; [4]Rwanda Biomedical Center, Kigali, Rwanda

701 Revaccinating HIV+ Adults With Double vs Standard HBV Regimen: ANRS B-BOOST Trial

David Rey[1]; Cécilie Dufour[2]; Marie-Josée Wendling[3]; Patrick Miailhes[4]; Philippe Sogni[8]; Georges Haour[2]; Marie-Louise Michel[7]; Lionel Piroth[6]; Odile Launay[5]; Fabrice Carrat[2]

[1]University Hospital Strasbourg, Strasbourg, France; [2]Université Pierre et Marie Curie, Strasbourg, France; [3]Hôpitaux Universitaires Strasbourg, Strasbourg, France; [4]University Hospital of Lyon, Lyon, France; [5]CIC Vaccinologie, Paris, France; [6]University Hospital of Dijon, Dijon, France; [7]Institut Pasteur, Paris, France; [8]Cochin Hospital, Paris, France

702 Complex HBV Quasispecies Affects Immunogenicity in Acute Hepatitis B Infection

Valentina Svicher[1]; Marianna Aragri[1]; Nicola Coppola[2]; Claudia Alteri[1]; Arianna Battisti[1]; Caterina Sagnelli[2]; Mariantonietta Pisaturo[2]; MariaConcetta Bellocchi[1]; Evangelista Sagnelli[2]; Carlo-Federico Perno[1]

[1]University of Rome Tor Vergata, Rome, Italy; [2]Second University of Naples, Naples, Italy

703 Higher Rate of Hepatitis B Antigen and Anti-HBV Antibody Seroconversion Among HIV/Chronic Hepatitis B Coinfection Initiating HBV Active HAART From Thailand

Anchalee Avihingsanon[1]; Opass Putcharoen[2]; Salyavit Chittmittrapap[2]; Tanakorn Apornpong[1]; Vorapot Sapsirisavat[1]; Sasiwimol Ubolyam[1]; Stephen J. Kerr[1]; Kiat Ruxrungtham[1]

On behalf of the HIV-NAT 105 Study Team

[1]HIV Netherlands Australia Thailand Research Collaboration, Thai Red Cross - AIDS Research Centre, Patumwan, Thailand; [2]Chulalongkorn University, Bangkok, Thailand

704 Occult HBV/HIV Coinfection and Validation of Cost-Effective NAT Pooling PCR

Shanmugam Saravanan[1]; Janardhanan Mohanakrishnan[1]; Thongadi Ramesh Dinesha[1]; Jayaseelan Boobalan[1]; Pachamuthu Balakrishnan[1]; Kailapuri G Murugavel[1]; Sunil S Solomon[2]; Suniti Solomon[1]; Davey M. Smith[3]

[1]YRG Centre for AIDS Research and Education, Chennai, India; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]University of California San Diego, San Diego, CA, US

705 Invariant Natural Killer T-Cells in HIV-HBV Coinfection

Matteo Basilissi[1]; Camilla Tincati[1]; Esther Merlini[1]; Elisabetta Sinigaglia[2]; Javier Sanchez-Martinez[2]; Giovanni Carpani[2]; Antonella d'Arminio Monforte[1]; Laura Milazzo[1]; Giulia Marchetti[1]

[1]University of Milan, Milan, Italy; [2]San Paolo Hospital, Milan, Italy

706 Effect of Immunosuppression and Antivirals on Intracellular HBV Replication in HIV-HBV Coinfection

Anders C. Boyd[1]; Karine Lacombe[1]; Fabien Lavocat[2]; Sarah Maylin[3]; Patrick Miailhes[4]; Caroline Lascoux-Combe[5]; Constance Delaugerre[3]; Pierre-Marie Girard[1]; Fabien Zoulim[2]

[1]Inserm UMR_S1136, Paris, France; [2]Inserm U1052, Lyon, France; [3]Inserm U941, Paris, France; [4]Hospices Civils de Lyon, Lyon, France; [5]Hôpital Saint-Louis AP-HP, Paris, France

707 Prevalence of HDV in a Midwestern HIV-HBV Coinfected Population

Sanam Razeghi; Susan Rouster; Kenneth E. Sherman

University of Cincinnati, Cincinnati, OH, US

708LB Oral Prenylation Inhibition With Lonafarnib in Chronic Hepatitis D Infection: A Randomized, Double-Blinded, Placebo-Controlled Proof-of-Concept Study

Christopher Koh[1]; Laetitia Canini[7]; Harel Dahari[2]; David Cory[3]; Ingrid Choong[3]; David Kleiner[4]; Stewart Cooper[6]; Mark A. Winters[5]; Jeffrey Glenn[5]; Theo Heller[1]

[1]National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Fulton, MD, US; [2]Loyola University Medical Center, Maywood, IL, US; [3]Eiger BioPharmaceuticals, San Carlos, CA, US; [4]National Cancer Institute, Bethesda, MD, US; [5]Stanford University, Stanford, CA, US; [6]California Pacific Medical Center, Palo Alto, CA, US; [7]University of Edinburgh, Edinburgh, United Kingdom

709 Incidence of Hepatitis E Virus in HIV-Infected Patients: A Longitudinal Prospective Study

Antonio Rivero-Juarez[1]; Loreto Martinez-Dueñas[1]; Antonio Martinez-Peinado[2]; Angela Camacho[1]; Celia Cifuentes[3]; Ana Gordon[1]; Mario Frias[1]; Julian Torre-Cisneros[1]; Juan A. Pineda[3]; Antonio Rivero[1]

[1]Instituto Maimonides de Investigación Biomédica de Córdoba, Cordoba, Spain; [2]Instituto Maimonides de Investigación Biomedica de Córdoba, Cordoba, Spain; [3]Hospital Universitario de Valme, Seville, Spain

TUESDAY, FEBRUARY 24, 2015

Session P-01 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HPV Infections and Cancers

710 Factors Associated With Extensive Cervical Lesions Among HIV-Infected Women Screening for AIDS Clinical Trials Group (ACTG) Protocol A5282

Timothy J. Wilkin[1]; Roy Matining[2]; Vikrant Sahasrabuddhe[3]; Catherine Godfrey[4]; Thandie Lungu[5]; Mulindi Mwanahamuntu[6]; Ramesh Bhosale[7]; Scott Evans[2]; Robert W. Coombs[8]; Cynthia Firnhaber[9]

[1]Weill Cornell Medical College, New York, NY, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Cambridge, MA, US; [3]National Cancer Institute (NCI), Bethesda, MD, US; [4]Division of AIDS (DAIDS), NIAID, NIH, Bethesda, MD, US; [5]University of North Carolina Project–Malawi, Lilongwe, Malawi; [6]University Teaching Hospital, Lusaka, Zambia; [7]Byramjee Jeejeebhoy Medical College, Pune, India; [8]University of Washington, Seattle, WA, US; [9]University of Witswatersand, Johannesburg, South Africa

711 HIV Infection and Survival Among Women With Cervical Cancer in Botswana

Scott Dryden-Peterson[1]; Memory Bvochora-Nsingo[2]; Heluf Medhin[3]; Gita Suneja[4]; Aida Asmelash[5]; Malebogo Pusoentsi[3]; Anthony Russell[6]; Jason Efstathiou[6]; Bruce Chabner[6]; Shahin Lockman[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Jamaica Plain, MA, US; [2]Gaborone Private Hospital, Gaborone, Botswana; [3]Botswana Ministry of Health, Gaborone, Botswana; [4]University of Utah, Salt Lake City, UT, US; [5]Botswana Harvard AIDS Institute, Gaborone, Botswana; [6]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

712 Potential Cost-Effectiveness of Cervical Cancer Screening of HIV-Positive Kenyan Women

Marita Mann; Joseph Babigumira; Louis Garrison; Michael Chung

University of Washington, Seattle, WA, US

713 Anal High-Risk Human Papillomavirus (HPV) Infection Among HIV-Infected MSM in the SUN Study, 2004-2011

Pragna Patel[1]; Tim Bush[1]; Erna Kojic[2]; Lois Conley[1]; Elizabeth Unger[1]; Teresa Darragh[3]; Keith Henry[4]; John Hammer[5]; Nur Onen[6]; Joel Palefsky[3]

[1]CDC, Atlanta, GA, US; [2]Brown University, Providence, RI, US; [3]University of California San Francisco, San Francisco, CA, US; [4]University of Minnesota, Minneapolis, MN, US; [5]Denver Infectious Diseases Consultants, Denver, CO, US; [6]Washington University School of Medicine, St. Louis, MO, US

714 Long-Term Effectiveness of Electrocautery Ablation of HGAIN in HIV-Infected MSM

Joaquin Burgos[1]; Adria Curran[1]; Natalia Tallada[1]; Ana Guelar[2]; Jordi Navarro[1]; Stefania Landolfi[1]; Judith Villar[2]; Manel Crespo[1]; Esteve Ribera[1]; Vicenç Falco[1]

[1]University Hospital Vall d'Hebron, Barcelona, Spain; [2]University Hospital del Mar, Barcelona, Spain

715 Survival and Treatment Trends for Squamous Cell Carcinoma of the Anus in HIV Infection

Robert A. Pitts; Stephen Goldstone; Keith Sigel; Michael M. Gaisa; Carlie Sigel; Juan Wisnivesky

Icahn School of Medicine at Mount Sinai, New York, NY, US

716 Oral HPV Shedding and Warts After Starting Antiretroviral Therapy: ACTG Protocol A5272

Caroline H. Shiboski[1]; Anthony Lee[2]; Jennifer Webster-Cyriaque[3]; Huichao Chen[2]; Malcolm John[1]; Raphael J. Landovitz[4]; Mark Jacobson[1]

Oral HIV/AIDS Research Alliance and the AIDS Clinical Trial Group

[1]University of California San Francisco, San Francisco, CA, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]University of North Carolina, Chapel Hill, NC, US; [4]University of California Los Angeles, Los Angeles, CA, US

717 Excess Risk of Rectal Squamous Cell Carcinoma in HIV-Infected Persons

Anna E. Coghill; Meredith S. Shiels; Eric A. Engels

National Cancer Institute, Rockville, MD, US

WEDNESDAY, FEBRUARY 25, 2015

Session P-02 Poster Session — Poster Hall

2:30 pm – 4:00 pm

AIDS-Related Cancers: Lymphoma and KS

718 Incidence and Outcomes of HIV-Associated Lymphomas in Botswana

Michael G. Milligan[1]; Elizabeth Bigger[3]; Musimar Zola[7]; Mukendi Kayembe[6]; Heluf Medhin[5]; Gita Suneja[4]; Shahin Lockman[2]; Jeremy Abramson[3]; Bruce Chabner[3]; Scott Dryden-Peterson[2]

[1]Harvard Medical School, Brookline, MA, US; [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [4]University of Utah, Salt Lake City, UT, US; [5]Botswana Ministry of Health, Gaborone, Botswana; [6]Botswana National Health Laboratory, Gaborone, Botswana; [7]Princess Marina Hospital, Gaborone, Botswana

719 CHOP Is Feasible for HIV-Associated Lymphoma in the ART Era in Malawi

Satish Gopal[2]; Yuri Fedoriw[1]; Agnes Moses[2]; Nathan Montgomery[1]; Wongani Kaimila[2]; Coxcilly Kampani[2]; Robert Krysiak[2]; Kristy Richards[1]; Thomas Shea[1]; George Liomba[2]

[1]University of North Carolina, Chapel Hill, NC, US; [2]University of North Carolina Project–Malawi, Lilongwe, Malawi

720 Chronic Hepatitis B and C Infection and Risk for Non-Hodgkin Lymphoma in HIV-Infected Patients

Heiner C. Bucher

On behalf of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord

University Hospital Basel, Basel, Switzerland

721 HIV-Associated Kaposi Sarcoma Treated With Chemotherapy and ART in Rural Malawi

Michael E. Herce[1]; Noel Kalanga[2]; Jonathan T. Crocker[2]; Emily B. Wroe[2]; James W. Keck[2]; Felix D. Chingoli[3]; Satish Gopal[1]; Junior Bazile[2]; Jason A. Beste[2]; Jonas Rigodon[2]

[1]University of North Carolina, Chapel Hill, NC, US; [2]Partners In Health, Neno, Malawi; [3]Ministry of Health of the Republic of Malawi, Neno, Malawi

722 High Mobility Group Box 1 (HMGB1) and HIV-Associated Kaposi Sarcoma in Africa

Helen Byakwaga[1]; Peter W. Hunt[3]; Miriam O. Laker-Oketta[2]; Albert R. Davalos[6]; Conrad Muzoora[1]; David V. Glidden[3]; A. Rain Mocello[3]; David R. Bangsberg[4]; Edward Mbidde[5]; Jeffrey N. Martin[3]

[1]Mbarara University of Science and Technology, Mbarara, Uganda; [2]Infectious Diseases Institute, Kampala, Uganda; [3]University of California San Francisco, San Francisco, CA, US; [4]Massachusetts General Hospital, Center for Global Health, Harvard Medical School, Boston, MA, US; [5]Uganda Virus Research Institute, Entebbe, Uganda; [6]Buck Institute for Research on Aging, Novato, CA, US

723 The CXCL12/CXCR4-CXCR7 Pathway, a Trio Implicated in Kaposi Sarcoma Pathogenesis

Aude Desnoyer[2]; Francoise Gaudin[2]; Agnes Carlotti[3]; Nicolas Dupin[3]; Francois Boue[2]; Karl Balabanian[2]; **Valérie Martinez-Pourcher**[1]

[1]Hopital Pitié-Salpêtrière, Paris, France; [2]Inserm, Univ Paris-Sud, LABEX LERMIT, UMR_S996, Clamart, France; [3]Dermatology, Paris, France

THURSDAY, FEBRUARY 26, 2015

Session P-03 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Cancer and Cancer Risk in HIV Subpopulations and Lung Cancer

724 Cancer in HIV-Infected Children: Record Linkage Study in South Africa

Julia Bohlius[6]; Nicky Maxwell[2]; Brian Eley[3]; Hans Prozesky[4]; Shobna Sawry[1]; Karl-Günter Technau[1]; Alan Davidson[2]; Cristina Stefan[5]; **Matthias Egger**[6]

On behalf of IeDEA Southern Africa

[1]University of the Witwatersrand, Johannesburg, South Africa; [2]University of Cape Town, Cape Town, South Africa; [3]Red Cross War Memorial Children's Hospital, Cape Town, South Africa; [4]University of Stellenbosch and Tygerberg Academic Hospital, Cape Town, South Africa; [5]Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa; [6]University of Bern, Bern, Switzerland

725 High Cancer Risk Among the HIV-Infected Elderly in the United States

Elizabeth L. Yanik; Hormuzd A. Katki; Eric A. Engels

National Cancer Institute (NCI), Rockville, MD, US

726 Smoking Outweighs HIV-Related Risk Factors for Non–AIDS-Defining Cancers

Keri N. Althoff[1]; Stephen J. Gange[1]; Chad Achenbach[2]; Lisa P. Jacobson[1]; Angel M. Mayor[3]; Michael J. Silverberg[4]; Amy Justice[5]; Richard Moore[6]; Yuezhou Jing[1]; Kelly Gebo[6]
On behalf of the North American AIDS Cohort Collaboration on Research and Design

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [3]Universidad Central del Caribe, Bayamon, US; [4]Kaiser Permanente Northern California, Oakland, CA, US; [5]Veterans Affairs Connecticut Healthcare System and Yale Schools of Medicine and Public Health, New Haven, CT, US; [6]Johns Hopkins University School of Medicine, Baltimore, MD, US

727 High Frequency of Early Lung Cancer Diagnosis With Chest CT in HIV-Infected Smokers

Alain Makinson[1]; Sabrina Eymard-Duvernay[2]; François Raffi[3]; Fabrice Bonnet[4]; Laurence Thirard[5]; Pierre Tattevin[6]; Sophie Abgrall[7]; Jacques Reynes[1]; Vincent Le Moing[1]
on behalf of the ANRS EP48 HIV CHEST Study Team

[1]University Hospital Montpellier, UMI233, Montpellier, France; [2]UMI 233, IRD, University Montpellier 1, Montpellier, France; [3]Nantes University Hospital, Nantes, France; [4]University Hospital Bordeaux, Inserm U897, Bordeaux, France; [5]Tourcoing University Hospital, Tourcoing, France; [6]Pontchaillou University Hospital, Rennes, France; [7]University Hospital Avicennes, Bobigny, France; [8]ANRS, Paris, France

728 CD4 Measures as Predictors of Lung Cancer Risk and Prognosis in HIV Infection

Keith Sigel[1]; Kristina Crothers[2]; Kirsha Gordon[3]; Sheldon Brown[4]; David Rimland[5]; Maria Rodriguez-Barradas[6]; Cynthia Gibert[7]; Matthew B. Goetz[8]; Roger Bedimo[9]; Robert Dubrow[10]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, US; [2]University of Washington School of Medicine, Seattle, WA, US; [3]VA Connecticut Healthcare System and Yale University Schools of Medicine and Public Health, New Haven, CT, US; [4]James J. Peters VA Medical Center, Bronx, NY, US; [5]Atlanta VA Medical Center, Atlanta, GA, US; [6]Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, US; [7]Washington DC Veterans Affairs Medical Center, Washington, DC, US; [8]Los Angeles VA Medical Center, Los Angeles, CA, US; [9]Veterans Affairs North Texas Health Care System, Dallas, TX, US; [10]Yale University School of Public Health, New Haven, CT, US

TUESDAY, FEBRUARY 24, 2015

Session P-P1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Cardiovascular Disease Outcomes

729 Cardiovascular Disease Mortality Among HIV-Infected Persons, New York City, 2001–2012

David B. Hanna[1]; Chitra Ramaswamy[2]; Robert C. Kaplan[1]; Regina Zimmerman[2]; Sarah L. Braunstein[2]

[1]Albert Einstein College of Medicine, Bronx, NY, US; [2]New York City Department of Health and Mental Hygiene, Long Island City, NY, US

730 Angiographic Restenosis After PTCA in HIV-Infected Patients: Incidence and Predictors

Dominik Promny[3]; **Christoph D. Spinner**[1]; Salvatore Cassese[2]; Isabell Bernlochner[3]; Christian Bradaric[3]; Karl-Ludwig Laugwitz[3]; Adnan Kastrati[2]; Simon Schneider[3]

[1]University Hospital Klinikum Rechts der Isar, Munich, Germany; [2]Deutsches Herzzentrum Muenchen, Munich, Germany; [3]University Hospital Klinikum Rechts der Isar, Munich, Germany

WEDNESDAY, FEBRUARY 25, 2015

Session P-P2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Dyslipidemia: Mediators and Treatment

731 PCSK9 Is Elevated in HIV+ Patients and May Mediate HIV-Associated Dyslipidemia

Payal Kohli[1]; Peter Ganz[1]; Yifei Ma[1]; Rebecca Scherzer[1]; Kristinalisa Maka[1]; Scott Wasserman[2]; Rob Scott[2]; Priscilla Hsue[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Amgen, Thousand Oaks, CA, US

732 Enhanced, Not Inhibited Monocyte Cholesterol Efflux Characterises Untreated HIV

Jane A. O'Halloran[2]; Therese Herlihy[2]; Alan Macken[2]; Louise Rainford[2]; John S. Lambert[2]; Gerard J. Sheehan[2]; Niall G. Mahon[2]; Leo P. Lawler[2]; Patrick W. Mallon[2]

[1]University College Dublin, Dublin, Ireland; [2]University College Dublin, Dublin, Ireland; [3]University College Dublin, Dublin, Ireland; [4]University College Dublin, Dublin, Ireland; [5]University College Dublin, Dublin, Ireland

733 Rosuvastatin vs Protease Inhibitor Switch for Hypercholesterolemia: Randomised Trial

Frederick J. Lee[7]; Polyana Monteiro[3]; David Baker[1]; Mark Bloch[2]; Robert Finlayson[8]; Richard Moore[5]; Norman Roth[6]; Jennifer F. Hoy[4]; Esteban Martinez[3]; Andrew Carr[7]

[1]East Sydney Doctors, Sydney, Australia; [2]Holdsworth House Medical Practice, Sydney, Australia; [3]Hospital Clinic, University of Barcelona, Barcelona, Spain; [4]Monash University/Alfred Hospital, Melbourne, Australia; [5]Northside Clinic, Melbourne, Australia; [6]Prahran Market Clinic, Melbourne, Australia; [7]St. Vincent's Hospital, Sydney, Australia; [8]Taylor Square Private Clinic, Sydney, Australia

734 Application of New ACC/AHA Cholesterol Guidelines to an HIV Clinical Care Cohort

Mosepele Mosepele[4]; Susan Regan[1]; James B. Meigs[1]; Steven Grinspoon[1]; Virginia A. Triant[1]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [4]Harvard School of Public Health, Boston, MA, US

Session P-P3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

ART: Cardiovascular Risk and Hypertension

735 ICAM-1 Overexpression Induced by Abacavir is Mediated by $P2X_7$ Receptors

Carmen de Pablo; Victor Collado-Diaz; Samuel Orden; Cesar Rios-Navarro; Juan Esplugues; **Angeles Alvarez**

University of Valencia, Valencia, Spain

736 Changes in Platelet Function Following Abacavir Administration: A Pilot Study

Janine M. Trevillyan[2]; Elizabeth E. Gardiner[2]; Jane F. Arthur[2]; Jing Jing[2]; Robert K. Andrews[2]; Jennifer F. Hoy[2]

[1]Monash University, Melbourne, Australia; [2]Monash University, Melbourne, Australia

737 An RCT of Rilpivirine vs Efavirenz on Cardiovascular Risk in Healthy Volunteers

Samir K. Gupta[1]; James E. Slaven[1]; Ziyue Liu[1]

[1]Indiana University School of Medicine, Indianapolis, IN, US; [2]Indiana University, School of Medicine, Indianapolis, IN, US

738 Elvitegravir Reduces Monocyte Activation and Vascular Inflammation More Than Efavirenz

Corrilynn O. Hileman[1]; Bruce Kinley[1]; Valeska Scharen-Guivel[2]; Kathy Melbourne[2]; Javier Szwarcberg[2]; Janet Robinson[1]; Michael M Lederman[1]; Grace A. McComsey[1]

[1]Case Western Reserve University, Cleveland, OH, US; [2]Gilead Sciences, Inc., Foster City, CA, US

739 Impact of Antiretroviral Drugs on Hypertension in HIV-Positive Persons: D:A:D Study

Camilla I. Hatleberg[1]; Lene Ryom[1]; Antonella d'Arminio Monforte[2]; Eric Fontas[3]; Peter Reiss[4]; Ole Kirk[1]; Wafaa M. El-Sadr[5]; Stéphane De Wit[6]; Jens D. Lundgren[1]; Caroline Sabin[7]
On behalf of the D:A:D Study group

[1]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [2]San Paolo University Hospital, Milan, Italy; [3]Nice University Hospital, Nice, France; [4]Academic Medical Center, University of Amsterdam, Amstredam, Netherlands; [5]Columbia University, New York, NY, US; [6]Centre Hospitalier Universitaire St. Pierre Hospital, Brussels, Belgium; [7]University College London, London, United Kingdom

740 Population-Based Assessment of Hypertension Among HIV Patients in Rural Uganda

Dalsone Kwarisiima[1]; Prashant Kotwani[3]; Norton Sang[4]; Florence Mwangwa[2]; Vivek Jain[3]; Dathan Byonanebye[2]; James Ayieko[4]; Laura Balzer[5]; Diane Havlir[3]; Moses R. Kamya[6]

[1]Makerere University Joint AIDS Program, Kampala, Uganda; [2]Infectious Disease Research Collaboration, Kampala, Uganda; [3]University of California San Francisco, San Francisco, CA, US; [4]Research Care Training Program, Kenya Medical Research Institute, Nairobi, Kenya; [5]University of Berkeley, Berkeley, CA, US; [6]Makerere University College of Health Sciences, Kampala, Uganda

TUESDAY, FEBRUARY 24, 2015

Session P-P4 Poster Session — Poster Hall

2:30 pm – 4:00 pm

What Predicts Risk for CVD in HIV?

741 CD4/CD8 Ratio, Age, and Serious Noninfectious Outcomes in HIV-Infected Adults

Jessica L. Castilho; Megan Turner; Sally Bebawy; Bryan E. Shepherd; Timothy Sterling

Vanderbilt University School of Medicine, Nashville, TN, US

742 Relationship Between Confirmed eGFR and Cardiovascular Disease in HIV-Positive Persons

Lene Ryom[1]; Jens D. Lundgren[1]; Peter Reiss[2]; Michael Ross[3]; Christoph Fux[4]; Philippe Morlat[7]; Olivier Moranne[5]; Colette Smith[6]; Caroline Sabin[6]; Amanda Mocroft[6]
On Behalf of the D:A:D Study Group

[1]CHIP, Department of Infectious Diseases and Rheumatology, Rigshospitalet and University of Copenhagen, Copenhagen, Denmark; [2]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; [3]Division of Nephrology, Mount Sinai School of Medicine, New York, New York City, NY, US; [4]Clinic for Infectious Diseases and Hospital Hygiene, Kantonsspital Aarau, Aarau, Switzerland; [5]Nephrology department, Public Health department, CHU Nice, Nice, France; [6]University College London, London, United Kingdom; [7]University of Bordeaux, INSERM U 897, CHU de Bordeaux, Bordeaux, France

743 Smoking, Other Substance Use and Coronary Atherosclerosis Among HIV-Infected and Uninfected Men

Sean G. Kelly[1]; Michael Plankey[3]; Wendy Post[2]; Xiuhong Li[2]; Ron Stall[4]; Lisa P. Jacobson[2]; Mallory Witt[5]; Lawrence Kingsley[4]; Christopher Cox[2]; Frank J. Palella[1]

[1]Northwestern University, Chicago, IL, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]Georgetown University, Washington, DC, US; [4]University of Pittsburgh, Pittsburgh, PA, US; [5]University of California Los Angeles, Los Angeles, CA, US

744 Pericardial Fat Density: A Novel Marker of Cardiometabolic Risk in HIV Infection

Chris T. Longenecker; Mark Schlucter; Yiying Liu; Grace A. McComsey

Case Western Reserve University, Cleveland, OH, US

745 The Effect of Physical Activity on Cardiometabolic Health and Inflammation in HIV

Sahera Dirajlal-Fargo[1]; Allison R. Webel[2]; Bruce Kinley[3]; Danielle Labbato[3]; Ying Jiang[4]; Sara M. Debanne[4]; Grace A. McComsey[1]

[1]Rainbow Babies and Children's Hospital, Case Western Reserve University School of Medicine, Cleveland, OH, US; [2]Frances Payne Bolton School of Nursing Case Western Reserve University, Cleveland, OH, US; [3]University Hospitals Case Medical Center, Cleveland, OH, US; [4]Case Western Reserve University, Cleveland, OH, US

WEDNESDAY, FEBRUARY 25, 2015

Session P-P5 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Cardiovascular Risk Prediction

746 Cumulative HIV Care Measures Highly Associated With Acute Myocardial Infarction

Jorge L. Salinas[1]; Christopher T. Rentsch[2]; Vincent C. Marconi[1]; Janet Tate[3]; Adeel A. Butt[4]; Matthew S. Freiberg[4]; Matthew B. Goetz[5]; Maria Rodriguez-Barradas[6]; Amy Justice[3]; David Rimland[1]

[1]Emory University, Atlanta, GA, US; [2]Atlanta VA Hospital, Decatur, GA, US; [3]Yale University, New Haven, CT, US; [4]University of Pittsburgh, Pittsburgh, PA, US; [5]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US; [6]Baylor College of Medicine, Houston, TX, US

747 Cardiovascular Disease Risk Prediction in the HIV Outpatient Study (HOPS)

Angela M. Thompson-Paul[1]; **Kenneth A. Lichtenstein**[2]; Carl Armon[3]; Kate Buchacz[1]; Rachel Debes[3]; Joan S. Chmiel[4]; Frank J. Palella[4]; Stanley C. Wei[1]; Jacek Skarbinski[1]; John T. Brooks[1]

[1]US Centers for Disease Control and Prevention, Atlanta, GA, US; [2]National Jewish Health, Denver, CO, US; [3]Cerner Corporation, Vienna, VA, US; [4]Northwestern University, Feinberg School of Medicine, Chicago, IL, US

748 Incidence and Risk of Myocardial Infarction (MI) by Type in the NA-ACCORD

Daniel R. Drozd[1]; Mari M. Kitahata[1]; Keri N. Althoff[2]; Jinbing Zhang[2]; Susan R. Heckbert[1]; Matthew J. Budoff[3]; Frank J. Palella[4]; Daniel B. Klein[5]; Richard D. Moore[6]; Heidi M. Crane[1]

[1]University of Washington, Seattle, WA, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]University of California Los Angeles, Los Angeles, CA, US; [4]Northwestern University, Chicago, IL, US; [5]Kaiser Permanente Northern California, Hayward, CA, US; [6]Johns Hopkins University, Baltimore, MD, US

749LB Abacavir Use and Risk for Myocardial Infarction in the NA-ACCORD

Frank J. Palella[1]; Keri N. Althoff[2]; Richard Moore[3]; Jinbing Zhang[2]; Mari Kitahata[4]; Stephen J. Gange[2]; Heidi M. Crane[4]; Daniel R. Drozd[4]; John T. Brooks[5]; Richard Elion[6]

[1]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]Johns Hopkins University, Baltimore, MD, US; [4]University of Washington, Seattle, WA, US; [5]US Centers for Disease Control and Prevention, Atlanta, GA, US; [6]George Washington University, Washington, DC, US

750 HIV-Infected Veterans and the New ACC/AHA Cholesterol Guidelines: Got Statins?

Meredith E. Clement[1]; Lawrence Park[1]; Ann Marie Navar-Boggan[1]; Nwora L. Okeke[1]; Michael Pencina[1]; Pamela Douglas[1]; Susanna Naggie[1]

[1]Duke University, Durham, NC, US; [2]Duke University, Durham, NC, US; [3]Duke University, Durham, NC, US

751 Evaluation of the ACC/AHA CVD Risk Prediction Algorithm Among HIV-Infected Patients

Susan Regan[2]; James B. Meigs[2]; Joseph Massaro[3]; Ralph B. D'Agostino[3]; Steven Grinspoon[2]; **Virginia A. Triant**[2]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Boston University, Boston, MA, US; [4]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

TUESDAY, FEBRUARY 24, 2015

Session P-P6 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Biomarkers and Atherosclerosis

752 IL-6 and CD8 Senescence Independently Associate With Atherosclerosis in Treated HIV

Denise C. Hsu[1]; Zonghui Hu[1]; Courtney Carroll[2]; Kristinalisa Maka[2]; Adam Rupert[3]; Steven Deeks[2]; S. C. Kalapus[2]; Priscilla Hsue[2]; Irini Sereti[1]

[1]National Institute of Allergy and Infectious Diseases, Bethesda, MD, US; [2]University of California San Francisco, San Francisco, CA, US; [3]Leidos Biomedical Research, Inc, Frederick, MD, US

753 sCD163 Correlates With IMT and Macrophages in Aorta and Heart With HIV Infection

Joshua A. Walker[1]; Graham A. Beck[1]; Andrew D. Miller[2]; Tricia H. Burdo[1]; Kenneth C. Williams[1]

[1]Boston College, Chestnut Hill, MA, US; [2]Cornell University, Ithaca, NY, US

754 Non-Classical Monocytes Predict Progression of Carotid Intima-Media Thickness

Dominic C. Chow[1]; Jamie M. Kagihara[1]; Guangxiang G. Zhang[1]; Scott A. Souza[1]; Brooks I. Mitchell[1]; Beau K. Nakamoto[1]; Kalpana J. Kallianpur[1]; Robert J. Matyas[2]; Lishomwa C. Ndhlovu[1]; Cecilia M. Shikuma[1]

[1]University of Hawaii, Honolulu, HI, US; [2]Kaiser Permanente, Honolulu, HI, US

755 TMAO and HIV-Associated Atherosclerosis

Arjun Sinha[1]; Yifei Ma[1]; Rebecca Scherzer[2]; Courtney Carroll[1]; Steven Deeks[3]; Peter Ganz[1]; Priscilla Hsue[1]

[1]San Francisco General Hospital, San Francisco, CA, US; [2]San Francisco VA Medical Center, San Francisco, CA, US; [3]University of California San Francisco, San Francisco, CA, US

756 Impaired Cardiac Strain and Biomarkers of Immune Activation in HIV

Colleen Hadigan[1]; **Julia Purdy**[1]; Diana Thiara[1]; Louisa Howard[1]; Chia-Ying Liu[1]; Fabio Raman[1]; Sabrina Mangat[1]; Christopher Sibley[2]; David Bluemke[1]

[1]National Institutes of Health (NIH), Bethesda, MD, US; [2]Oregon Health and Sciences University, Portland, OR, US

Session P-P7 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Endothelial Functions and Cerebral Vasoreactivity

757 Role of Angiopoietin 1, Angiopoietin 2, and Endothelial Function in HIV

Mark L. Dela Cruz[1]; Yifei Ma[1]; Rebecca Scherzer[1]; Alan Wu[2]; Kristinalisa Maka[1]; Steven Deeks[1]; Peter Ganz[1]; Priscilla Hsue[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Blood Systems Research Institute/ University of California San Francisco, San Francisco, CA, US

758 HIV-Infected Persons With Type 2 Diabetes Have Evidence of Endothelial Dysfunction

Malene Hove[1]; Julie C. Gaardbo[3]; Hedda Hoel[3]; Lillian Kolte[2]; Allan Vaag[1]; Jan Gerstoft[1]; Henrik Ullum[1]; Marius Troseid[3]; Susanne D. Poulsen[1]

[1]Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark; [2]Hvidovre Hospital, University Hospital of Copenhagen, Hvidovre, Denmark; [3]Oslo University Hospital, Ullevål, Norway

759 Unique Circulating MicroRNA Profiles and Endothelial Function in HIV Infection

Venkata A. Narla[1]; Nirav Bhakta[2]; Jane E. Freedman[3]; Kahraman Tanriverdi[3]; Kristinalisa Maka[1]; Steven Deeks[2]; Peter Ganz[1]; Priscilla Hsue[1]

[1]San Francisco General Hospital, University of California San Francisco, San Francisco, CA, US; [2]University of California San Francisco, San Francisco, CA, US; [3]University of Massachusetts Medical School, Worcester, MA, US

760 Cerebral Vasoreactivity Is Impaired in Virally Suppressed HIV-Infected Individuals

Felicia C. Chow[1]; Claire Mills[1]; Nerissa Ko[1]; Courtney Carroll[1]; Richard Price[1]; Steven Deeks[1]; Farzaneh A. Sorond[2]; Priscilla Y. Hsue[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US

Session P-Q1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Inflammation: Biomarkers and Relationship to Outcomes

761 IL-6 Is a Stronger Predictor of Clinical Events Than hsCRP or D-Dimer in HIV Disease

Álvaro H. Borges[1]; Jemma L. O'Connor[2]; Andrew N. Phillips[2]; James D. Neaton[3]; Birgit Grund[4]; Jacqueline Neuhaus[3]; Michael Vjecha[7]; Alexandra Calmy[5]; Kersten K. Koelsch[6]; Jens D. Lundgren[1]

INSIGHT SMART and ESPRIT Study Groups

[1]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [2]University College London, London, United Kingdom; [3]University of Minnesota, Minneapolis, MN, US; [4]University of Minnesota, Minneapolis, MN, US; [5]Geneva University Hospitals, Geneva, Switzerland; [6]University of New South Wales, Sydney, Australia; [7]Veterans Affairs Medical Center, Washington, DC, US

762 Persistent Inflammation on ART Is Associated With Poor Nutritional Recovery in Zambia

George Praygod[2]; Meridith Blevins[1]; Susannah Woodd[3]; Andrea Rehman[3]; Jeremiah Kidola[2]; Henrik Friis[4]; Paul Kelly[5]; Douglas Heimburger[1]; Suzanne Filteau[3]; **John Koethe**[1]

[1]Vanderbilt University, Nashville, TN, US; [2]National Institute of Medical Research, Mwanza, United Republic of Tanzania; [3]London School of Hygiene & Tropical Medicine, London, United Kingdom; [4]University of Copenhagen, Copenhagen, Denmark; [5]University Teaching Hospital, Lusaka, Zambia

763 Smoking and Obesity May Partially Explain the Inflammation and Morbidity Association

Supriya Krishnan[1]; Ronald Bosch[1]; Benigno Rodriguez[2]; Peter W. Hunt[3]; Cara C. Wilson[4]; Steven Deeks[3]; Michael M Lederman[2]; Alan Landay[5]; Carey Lumeng[6]; Allan Tenorio[7]

[1]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, US; [2]Division of Infectious Diseases and HIV Medicine, Case Western Reserve University School of Medicine, Cleveland, OH, US; [3]Positive Health Program, Dept of Medicine, San Francisco General Hospital, San Francisco, CA, US; [4]Division of Infectious Diseases, Univ of Colorado Hospital, Aurora, CO, US; [5]Department of Immunology and Microbiology, Rush Univ Medical Center, Chicago, IL, US; [6]Univ of Michigan Medical School, Department of Pediatrics, Ann Arbor, MI, US; [7]Department of Medicine, Rush University Medical Center, Chicago, IL, US

764 Infectious and Noninfectious Multimorbidity Among HIV Clinic Clients in the African Cohort Study

Julie Ake[1]; Jonah Maswai[2]; Francis Kiweewa[3]; Lucas Maganga[4]; Milton Omondi[5]; Babajide Keshinro[6]; Lindsay Hughes[1]; Victor G. Valcour[7]; Christina Polyak[1]

RV 329 AFRICOS Study Team

[1]US Military HIV Research Program, Bethesda, MD, US; [2]KEMRI/Walter Reed Project, Kericho, Kenya; [3]Makerere University Walter Reed Project, Kampala, Uganda; [4]Mbeya Medical Research Centre, Mbeya, United Republic of Tanzania; [5]KEMRI/Walter Reed Project, Kisumu, Kenya; [6]Walter Reed Program - Nigeria, Abuja, Nigeria; [7]University of California San Francisco (UCSF), San Francisco, CA, US

Session P-Q2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Bone Metabolism and ART: Mechanisms and Outcomes

765 Bone Metabolism and Tenofovir: Evidence of Direct Effect on Calcium-Sensing Receptor

Paolo Bonfanti[2]; Caterina Brasacchio[3]; Chiara Molteni[2]; Barbara Menzaghi[1]; Laura Soldati[3]; Tiziana Quirino[1]; Stefano Mora[4]

[1]Busto Arsizio Hospital, Busto Arsizio, Italy; [2]A. Manzoni Lecco Hospital, Lecco, Italy; [3]Department of Health Sciences, University of Milan, Milan, Italy; [4]San Raffaele Scientific Institute, Milan, Italy

766 Bone Turnover on DRV/r + Either RAL or TDF/FTC as First-Line ART: NEAT 001 / ANRS 143

Jose I Bernardino[1]; Amanda Mocroft[2]; Laura Richert[3]; Abdel Babiker[4]; Antonio Buño[1]; Antonella Castagna[5]; Pierre-Marie Girard[6]; Genevieve Chene[3]; Jose R Arribas[1]; François Raffi[7]

[1]Hospital Universitario La Paz. IdiPAZ, Madrid, Spain; [2]University College London, London, United Kingdom; [3]University of Bordeaux, Bordeaux, France; [4]MRC Clinical Trials Unit at University College London, London, United Kingdom; [5]San Raffaele Scientific Institute, Milan, Italy; [6]Hospital St Antoine and Inserm, Paris, France; [7]Université Nantes, Nantes, France

767 Tenofovir Replacement in Patients With Osteoporosis Increased Sclerostin Levels

Eugenia Negredo[3]; Adolfo Díez-Pérez[2]; Pere Domingo[4]; Nuria Pérez-Álvarez[6]; Mar Gutierrez[4]; Gracia Mateo[4]; Jordi Puig[1]; Patricia Echeverria[1]; Anna Bonjoch[1]; Bonaventura Clotet[5]

[1]LLuita Contra la Sida Foundation, Germans Trias i Pujol University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; [2]Hospital del Mar-IMIM, Universitat Autònoma de Barcelona and RETICEF, Instituto Carlos III Madrid, Barcelona, Spain; [3]LLuita Contra la Sida Foundation, Germans Trias i Pujol University Hospital, Universitat Autònoma de Barcelona, Universitat de Vic–Universitat Central de Catalunya, Barcelona, Spain; [4]Santa Creu i Sant Pau Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; [5]LLuita Contra la Sida Foundation, Germans Trias i Pujol University Hospital, Universitat Autònoma de Barcelona, Irsicaixa Foundation, Germans Trias i Pujol University Hospital, Barcelona, Spain; [6]LLuita Contra la Sida Foundation, Germans Trias i Pujol University Hospital, Universitat Autònoma de Barcelona, Statistics and Operations Research Department, Universitat Politècnica de Catalunya, Barcelona, Spain

768 Relationship Between Phosphate Reabsorption, Age, Tenofovir and Bone Mineral Density

Lisa Hamzah[2]; **Amanda Samarawickrama**[1]; Karen Walker-Bone[3]; Yvonne Gilleece[4]; Martin Fisher[1]; Frank A. Post[5]

[1]Brighton and Sussex Medical School, London, United Kingdom; [2]King's College London, London, United Kingdom; [3]University of Southampton, Southampton, United Kingdom; [4]Brighton and Sussex Hospitals NHS Trust, Brighton, United Kingdom; [5]King's College Hospital NHS Foundation Trust, London, United Kingdom

769LB Less Bone Loss With a Maraviroc Regimen in HIV-Infected Treatment-Naïve Subjects

Babafemi Taiwo[1]; Ellen Chan[2]; Carl Fichtenbaum[3]; Heather Ribaudo[2]; Athe Tsibris[4]; Karin Klingman[5]; Joseph J. Eron[6]; Baiba Berzins[1]; Todd T. Brown[7]
ACTG A5303 Study Team

[1]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [2]Statistical and Data Analysis Center, Harvard School of Public Health, Boston, MA, US; [3]University of Cincinnati, Cincinnati, OH, US; [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [5]National Institutes of Health, Bethesda, MD, US; [6]University of North Carolina at Chapel Hill, Chapel Hill, NC, US; [7]Johns Hopkins University School of Medicine, Baltimore, MD, US

Session P-Q3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Bone Disease: Mechanisms of Bone Loss and Fracture Risk

770 Association of Adipokines With Bone Mineral Density in HIV+ and HIV- Women

Anjali Sharma[1]; Yifei Ma[2]; Rebecca Scherzer[2]; Amber L. Wheeler[2]; Mardge Cohen[3]; Deborah Gustafson[4]; Michael T Yin[5]; Phyllis C. Tien[2]

[1]Albert Einstein College of Medicine, Bronx, NY, US; [2]University of California San Francisco, San Francisco, CA, US; [3]John H. Stroger Jr. Hospital of Cook County, Chicago, IL, US; [4]State University of New York Downstate Medical Center, Brooklyn, NY, US; [5]College of Physicians and Surgeons, Columbia University, New York, NY, US

771 Long-Term Changes in Bone Mineral Density and Insulin Resistance on Statins in HIV

Kristine M. Erlandson[1]; Ying Jiang[2]; Sara M. Debanne[2]; Grace A. McComsey[2]

[1]University of Colorado, Aurora, CO, US; [2]Case Western Reserve University, Cleveland, OH, US

772 Immunologic Predictors of Bone Loss in a Contemporary HIV Cohort

Edgar T. Overton[1]; Katherine H. Hullsiek[2]; Gerome Escota[3]; Kenneth A. Lichtenstein[4]; Lois Conley[5]; Pragna Patel[5]; John T. Brooks[5]; Irini Sereti[6]; Jason V. Baker[2]
the CDC SUN (Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy) Investigators

[1]University of Alabama at Birmingham, Birmingham, AL, US; [2]University of Minnesota, Minneapolis, MN, US; [3]Washington University School of Medicine, St. Louis, MO, US; [4]National Jewish Health, Denver, CO, US; [5]Division of HIV/AIDS Prevention, Atlanta, GA, US; [6]National Institute of Allergy and Infectious Disease (NIAID), Bethesda, MD, US

773 RANKL Predicts 96-Week BMD Changes in ATV/r Monotherapy: A MODAt Trial Sub-Study

Vincenzo Spagnuolo[1]; Marco Borderi[2]; Giuseppina Musumeci[2]; Laura Galli[1]; Camilla Tincati[3]; Stefano Rusconi[3]; Giovanni Guaraldi[4]; Alba Bigoloni[1]; Adriano Lazzarin[1]; Antonella Castagna[1]

[1]San Raffaele Scientific Institute, Milan, Italy; [2]Alma Mater Studiorum University of Bologna, Bologna, Italy; [3]University of Milan, Milan, Italy; [4]University of Modena and Reggio Emilia, Modena, Italy

774 Predictors of Longitudinal Change in Bone Mineral Density in a Cohort of HIV Positive and Negative Subjects

Willard Tinago[1]; Aoife Cotter[1]; Caroline Sabin[2]; Alan Macken[1]; Eoin Kavanagh[3]; Jennifer Brady[4]; Geraldine McCarthy[5]; Juliet Compston[6]; Patrick W. Mallon[1]
HIV UPBEAT Study Group

[1]University College Dublin, Dublin, Ireland; [2]Research Department of Infection and Poulation Health, London, United Kingdom; [3]Mater Misericordiae University Hospital, Dublin, Ireland; [4]Mater Misericordiae University Hospital, Dublin, Ireland; [5]Mater Misericordiae University Hospital, Dublin, Ireland; [6]University of Cambridge, London, United Kingdom

775 Fracture Incidence Is Increased in Aging HIV-Infected Women

Anjali Sharma[1]; Qiuhu Shi[2]; Donald R. Hoover[3]; Kathryn Anastos[1]; Phyllis C. Tien[4]; Mary A. Young[5]; Mardge Cohen[6]; Deborah Gustafson[7]; Michael T Yin[8]

[1]Albert Einstein College of Medicine, Bronx, NY, US; [2]New York Medical College, Valhalla, NY, US; [3]Rutgers University, Piscataway, NJ, US; [4]University of California San Francisco, San Francisco, CA, US; [5]Georgetown University, Washington D.C., DC, US; [6]John H. Stroger Jr. Hospital of Cook County, Chicago, IL, US; [7]State University of New York Downstate Medical Center, Brooklyn, NY, US; [8]College of Physicians and Surgeons, Columbia University, New York, NY, US

Session P-Q4 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Measuring Bone Density

776 Heel Quantitative Ultrasound to Cut Down on DXA Costs in HIV-infected Patients

Marilia R. Pinzone; Maria Gussio; Daniela Castronuovo; Adriana Di Gregorio; Benedetto M. Celesia; Bruno Cacopardo; Giuseppe Nunnari

University of Catania, Catania, Italy

777 Novel Radiographic Measures HRpQCT and HSA as Correlates of HIV-Associated Fractures

Darrell H. Tan[1]; Janet Raboud[2]; Leah Szadkowski[2]; Eva Szabo[4]; Hanxian Hu[4]; Queenie Wong[4]; Angela Cheung[4]; Sharon Walmsley[3]

[1]St. Michael's Hospital, Toronto, Canada; [2]Toronto General Research Institute, Toronto, Canada; [3]University Health Network, Toronto, Canada; [4]Centre for Excellence in Skeletal Health Assessment, Toronto, Canada

WEDNESDAY, FEBRUARY 25, 2015

Session P-Q5 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Fat Without Borders: Metabolic Complications in Resource-Limited Settings

778 Obesity and Inflammation in Resource-Diverse Settings of ART Initiation

Kristine M. Erlandson[1]; Nikhil Gupte[2]; Javier R. Lama[3]; Patcharaphan Sugandhavesa[4]; Thando Mwelase[5]; Ashwin Balagopal[2]; David Asmuth[6]; Thomas B. Campbell[1]; Amita Gupta[2]
On behalf of the A5175 and NWCS319 study team

[1]University of Colorado, Aurora, CO, US; [2]Johns Hopkins University, Baltimore, MD, US; [3]Impacta Peru Clinical Trials Unit, Lima, Peru; [4]Chiang Mai University, Chiang Mai, Thailand; [5]University of Witswatersrand, Johannesburg, South Africa; [6]University of California Davis, Sacramento, CA, US

779 Body Composition Outcomes at 96 Weeks in the SECOND-LINE RCT DXA Substudy

Mark A. Boyd[1]; Janaki Amin[1]; Patrick W. Mallon[2]; Jennifer F. Hoy[3]; Samuel Ferret[4]; Waldo Belloso[5]; Praphan Phanuphak[6]; Sean Emery[1]; David A. Cooper[1]
SECOND-LINE study group

[1]University of New South Wales Australia, Sydney, Australia; [2]University College Dublin, Dublin, Ireland; [3]Monash University/Alfred Hospital, Melbourne, Australia; [4]Hopital Saint Louis, Paris, France; [5]Hospital Italiano, Buenos Aires, Argentina; [6]Thai Red Cross AIDS Research Centre, Bangkok, Thailand

780 Bone Quality by Quantitative Ultrasound at the Radius Does Not Differ in ART-Naïve HIV+ and HIV- Rwandan Women

Eugene Mutimura[1]; Qiuhu Shi[2]; Donald R. Hoover[3]; Kathryn Anastos[4]; Emmanuel Rudakemwa[5]; Jean Claude Dusingize[1]; Jean D'Amour Sinayobye[1]; Michael T Yin[6]

[1]Regional Alliance for Sustainable Development, Kigali, Rwanda; [2]School of Health Sciences and Practice, New York Medical College, New York, NY, US; [3]State University of New Jersey, New Brunswick, NJ, US; [4]Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, US; [5]King Faisal Hospital, Kigali, Rwanda; [6]Columbia University Medical Center, New York, NY, US

781 Predictors and Outcomes of Incident High Cholesterol in Adults on ART in South Africa

Denise Evans[1]; Alana T. Brennan[2]; Faith Moyo[1]; David Spencer[3]; Kay Mahomed[3]; Mhairi Maskew[1]; Lawrence Long[1]; Sydney Rosen[2]; **Matt P. Fox**[2]

[1]University of the Witwatersrand, Johannesburg, South Africa; [2]Boston University, Boston, MA, US; [3]Right to Care, Johannesburg, South Africa

782 Metabolic Changes and Second-Line ART in Africa (2LADY/ANRS 12169 Trial)

Amandine Cournil[1]; Assane Diouf[3]; Sabrina Eymard-Duvernay[1]; Adrien Sawadogo[2]; Liliane Ayangma[4]; Louise Fortes-Deguenonvo[3]; Jean-Marc Mben[6]; Eric Delaporte[1]; Laura Ciaffi[1]; Sinata Koulla-Shiro[5]

[1]IRD/UM 1, Montpellier, France; [2]CHU Souro Sanou, Bobo Dioulasso, Burkina Faso; [3]CRCF, Dakar, Senegal; [4]Yaounde Military Hospital, Yaounde, Cameroon; [5]FMSB/University Yaounde 1, Yaounde, Cameroon; [6]ANRS Research Center, Yaounde, Cameroon

TUESDAY, FEBRUARY 24, 2015

Session P-Q6 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Aging: Frailty, Telomeres, and mtDNA

783 Frailty and Cause-Specific Hospitalization Among Persons Aging With HIV and Drug Use

Damani A. Piggott[1]; Abimereki D. Muzaale[1]; Shruti H. Mehta[1]; Ryan P. Westergaard[2]; Todd T. Brown[1]; Kushang V. Patel[3]; Sean X. Leng[1]; Gregory D. Kirk[1]

[1]Johns Hopkins University, Baltimore, MD, US; [2]University of Wisconsin, Madison, WI, US; [3]University of Washington, Seattle, WA, US

784 Association of HIV Viral Load and Shorter Telomere Length

Shawn Gogia; Jue Lin; Yifei Ma; Rebecca Scherzer; Elizabeth Blackburn; Ramin Farzaneh-Far; Steven Deeks; Priscilla Hsue

University of California San Francisco, San Francisco, CA, US

785 Novel Mechanisms of Nucleoside Analog Associated Mitochondrial DNA Mutation

Kristian Gardner; Patrick F. Chinnery; **Brendan A. Payne**

Newcastle University, Newcastle-upon-Tyne, United Kingdom

786 Balance Confidence Predicts Falls Better Than Physical Function Testing in HIV+ Men

Todd T. Brown[1]; Xiuhong Li[2]; Lisa P. Jacobson[2]; Jennifer Schrack[2]; Frank J. Palella[3]; Lawrence Kingsley[4]; Joseph B. Margolick[2]; Adrian Dobs[1]; Jordan Lake[5]; Keri N. Althoff[2]
MACS

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [4]University of Pittsburgh, Pittsburgh, PA, US; [5]University of California Los Angeles, Los Angeles, CA, US

Session P-Q7 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Diabetes and Other Endocrine Disorders

787 Vitamin D Supplementation Does Not Affect Metabolic Changes Seen With ART Initiation

Todd T. Brown[1]; Ellen Chan[2]; Edgar T. Overton[3]; Pablo Tebas[4]; Kathy Melbourne[5]; Royce Hardin[6]; Heather Ribaudo[2]; Michael T. Yin[7]
ACTG

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]University of Alabama at Birmingham, Birmingham, AL, US; [4]University of Pennsylvania, Philiadelphia, PA, US; [5]Gilead Sciences, Inc., Foster City, CA, US; [6]Duke University, Durham, NC, US; [7]College of Physicians and Surgeons, Columbia University, New York, NY, US

788 First-Line NRTIs and Risk of New Onset Diabetes in HIV-Infected Adults in Thailand

Prakit Riyaten[1]; Nicolas Salvadori[2]; Patrinee Traisathit[1]; Nicole Ngo-Giang-Huong[2]; Rapeepan Suaysod[2]; Guttiga Halue[3]; Naruepon Yutthakasemsunt[4]; Apichat Chutanunta[5]; Jacqueline Capeau[6]; Gonzague Jourdain[2]

[1]Chiang Mai University, Chiang Mai, Thailand; [2]Institut de Recherche Pour le Développement UMI 174-PHPT, Chiang Mai, Thailand; [3]Phayao Provincial Hospital, Phayao, Thailand; [4]Nong Khai Hospital, Nong Khai, Thailand; [5]Samutsakhon Hospital, Samutsakhon, Thailand; [6]Sorbonne University, Paris, France

789 Diabetes Mellitus Among HIV-Infected Adults in Care in the United States, 2009–2010

Alfonso C. Hernandez-Romieu

Emory University Rollins School of Public Health, Decatur, GA, US

790 Functional Vitamin D Deficiency With Initiation of Tenofovir-Based ART?

Evelyn Hsieh[1]; Liana Fraenkel[1]; Weibo Xia[2]; Yang Han[2]; Michael T Yin[3]; Karl Insogna[4]; Ting Zhu[2]; Taisheng Li[2]

[1]Yale University School of Medicine, New Haven, CT, US; [2]Peking Union Medical College Hospital, Beijing, China; [3]Columbia University Medical Center, New York, NY, US; [4]Yale University School of Medicine, New Haven, CT, US

791 Determinants of Parathyroid Hormone Levels in HIV-positive Tenofovir-treated Patients with Normal Renal Function

Letizia Marinaro; Andrea Calcagno; Jessica Cusato; Elisabetta Scarvaglieri; Marco Simiele; Maria Cristina Tettoni; Laura Trentini; Antonio D'Avolio; Giovanni Di Perri; Stefano Bonora

Unit of Infectious Diseases, Turin, Italy

THURSDAY, FEBRUARY 26, 2015

Session P-Q8 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Renal Dysfunction: ART and Biomarkers

792 Elevated Tenofovir Exposure via Intensive PK Monitoring Is Associated With Progressive Kidney Function Decline

Sanjiv M. Baxi[1]; Rebecca Scherzer[1]; Ruth M. Greenblatt[1]; Howard Minkoff[2]; Kathryn Anastos[5]; Mardge H. Cohen[4]; Mary A. Young[3]; Monica Gandhi[1]; Michael G. Shlipak[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]State University of New York Downstate Medical Center, Brooklyn, NY, US; [3]Georgetown University, Washington, DC, US; [4]John Stroger (formerly Cook County) Hospital, Chicago, IL, US; [5]Montefiore Medical Center, University Hospital for Albert Einstein College of Medicine, Bronx, NY, US

793 Impact of TDF+PI/r on Renal Function in Sub-Saharan Africa : 2LADY/ANRS 12169 Trial

Arsene Hema[1]; **Amandine Cournil**[2]; Laura Ciaffi[2]; Sabrina Eymard-Duvernay[2]; Assane Diouf[3]; Nestor Manga[4]; Vincent Le Moing[2]; Jacques Reynes[2]; Sinata Koulla-Shiro[5]; Eric Delaporte[2]

[1]CHU Souro Sanou, Bobo Dioulasso, Burkina Faso; [2]IRD/UM 1, Montpellier, France; [3]Le Centre Régional de Recherche et de Formation à la Prise en Charge Clinique de Fann, Dakar, Senegal; [4]Yaounde Military Hospital, Yaounde, Cameroon; [5]FMSB/University Yaounde 1, Yaounde, Cameroon

794 Renal Tubular Disease and the Relationship With Tenofovir and Atazanavir Exposure

Lisa Hamzah[1]; John Booth[2]; Catherine Horsfield[3]; Rachael Jones[4]; Jeremy Levy[5]; Deborah Williams[6]; Nadia Khatib[7]; Rachel Hilton[3]; John Connolly[2]; Frank A. Post[8]

[1]King's College London, London, United Kingdom; [2]University College London, London, United Kingdom; [3]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [4]Chelsea and Westminster Hospital, NHS Foundation Trust, London, United Kingdom; [5]Imperial College London, London, United Kingdom; [6]Brighton and Sussex Hospitals NHS Trust, London, United Kingdom; [7]Heart of England NHS Foundation Trust, Birmingham, United Kingdom; [8]King's College Hospital NHS Foundation Trust, London, United Kingdom

795 Safety of Tenofovir Alafenamide in Renal Impairment

Anton Pozniak[2]; Jose R Arribas[3]; Samir K. Gupta[4]; Frank A. Post[5]; Anchalee Avihingsanon[6]; Gordon Crofoot[7]; Kenneth A. Lichtenstein[8]; Moti Ramgopal[9]; Ploenchan Chetchotisakd[10]; **Marshall W. Fordyce**[1]

[1]Gilead Sciences Inc, Foster City, CA, US; [2]Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom; [3]Hospital Universitario La Paz, Madrid, Spain; [4]Indiana University School of Medicine, Indianapolis, IN, US; [5]King's College Hospital NHS Foundation Trust, London, United Kingdom; [6]HIV-NAT, Thai Red Cross AIDS Research Center and Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [7]Crofoot Research, Houston, TX, US; [8]National Jewish Health, Denver, CO, US; [9]Midway Research Center, Ft. Pierce, FL, US; [10]Khon Kaen University, Khon Kaen, Thailand

796 Elevated Nonclassical Monocytes and Urine Fibrotic Markers in HIV Albuminuria

Brooks I. Mitchell; Mary Margeret Byron; Roland C. Ng; Dominic C. Chow; Pichaya O-charoen; Lishomwa C. Ndhlovu; Cecilia M. Shikuma

University of Hawaii, Honolulu, HI, US

797 Kidney Dysfunction and Markers of Inflammation in the Multicenter AIDS Cohort Study

Alison G. Abraham[1]; Annie Darilay[2]; Heather McKay[1]; Joseph B. Margolick[1]; Michelle M. Estrella[3]; Frank J. Palella[4]; Robert Bolan[5]; Charles R. Rinaldo[6]; Lisa P. Jacobson[1]

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]AstraZeneca, Gaithersburg, MD, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [5]Los Angeles LGBT Center, Los Angeles, CA, US; [6]University of Pittsburgh, Pittsburgh, PA, US

Session P-Q9 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Renal Transplantation: Long-Term Outcomes

798 Risk Factors for Acute Allograft Rejection in HIV Positive Kidney Transplant Recipients

Esther N. Gathogo[1]; Mark Harber[2]; Sanjay R. Bhagani[2]; Joanne Baxter[3]; Vincent Lee[4]; Jeremy Levy[5]; Rachael Jones[6]; Rachel Hilton[7]; Graham Davies[1]; Frank A. Post[1]

[1]King's College London, London, United Kingdom; [2]Royal Free London NHS Foundation Trust, London, United Kingdom; [3]North Manchester General Hospital, Manchester, United Kingdom; [4]Central Manchester University Hospitals, Manchester, United Kingdom; [5]Imperial College Healthcare NHS Trust, London, United Kingdom; [6]Chelsea and Westminster Hospital, NHS Foundation Trust, London, United Kingdom; [7]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

799 Survival in HIV-Positive Transplant Recipients Compared to Matched Registry Controls

Michelle E. Roland[1]; Burc Barin[2]; Shirish Huprikar[3]; **Michael Wong**[4]; Emily Blumberg[5]; David Simon[6]; Margaret Ragni[7]; Don Stablein[2]; Peter Stock[1]
HIV-TR Study Team

[1]University of California San Francisco, San Francisco, CA, US; [2]EMMES Corporation, Rockville, MD, US; [3]Mount Sinai School of Medicine, New York, NY, US; [4]Beth Israel Deaconess Medical Center, Boston, MA, US; [5]University of Pennsylvania, Philadephia, PA, US; [6]Rush University Medical Center, Chicago, IL, US; [7]University of Pittsburgh, Pittsburgh, PA, US

Session P-Q10 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Pulmonary Disease

800 Risk Factors for Airflow Obstruction Among HIV+ Individuals in Nairobi, Kenya

Engi F. Attia[1]; Elizabeth Maleche-Obimbo[2]; Nelly Yatich[1]; Lillian Ndukwe[3]; Julia Njoroge[3]; Sameh Sakr[3]; Neveen El Antouny[3]; Fr. Mena Attwa[3]; Kristina Crothers[1]; Michael Chung[1]

[1]University of Washington, Seattle, WA, US; [2]University of Nairobi, Nairobi, Kenya; [3]Coptic Hope Center for Infectious Diseases, Nairobi, Kenya

801 Pulmonary Complications of HIV-1 in Youth: The PHACS AMP Study

William T. Shearer[1]; Erin Leister[2]; George Siberry[3]; Denise L. Jacobson[2]; Russell B. Van Dyke[4]; Hannah H. Peavy[5]; Suzanne Siminski[6]; Meyer Kattan[7]; Laurie Butler[6]; Andrew Colin[8]

[1]Baylor College of Medicine and Texas Children's Hospital, Houston, TX, US; [2]Harvard School of Public Health, Boston, MA, US; [3]National Institutes of Health (NIH), Bethesda, MD, US; [4]Tulane University Health Sciences Center, New Orleans, LA, US; [5]National Heart, Lung, and Blood Institute, Bethesda, MD, US; [6]Frontier Science and Technology Research Foundation, Amherst, NY, US; [7]Columbia University Medical Center, New York, NY, US; [8]University of Miami Health System Batchelor Research Institute, Miami, FL, US

802 Distinct Airway Methylation and Gene Expression Profiles in HIV-Associated COPD

Janice M. Leung[1]; Emily Vucic[2]; Joseph C. Liu[1]; David Ngan[1]; Tawimas Shaipanich[3]; Julio Montaner[4]; Stephen Lam[2]; Don Sin[1]; Wan Lam[2]; S. F. Paul Man[1]

[1]Centre for Heart Lung Innovation, Vancouver, Canada; [2]BC Cancer Research Center, Vancouver, Canada; [3]St. Paul's Hospital, Vancouver, Canada; [4]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada

Session P-Q11 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Body Composition and Risk Factors for Abnormalities

803 Altered Body Composition and Inflammation in HIV Infection With Type 2 Diabetes

Malene Hove; Julie Abildgaard; Julie C. Gaardbo; Allan Vaag; Jan Gerstoft; Bente Klarlund Pedersen; Birgitte Lindegaard; Susanne D. Poulsen

Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark

804 Alcohol, Substance Use, and Smoking Associations With Lipoatrophy and Lipohypertrophy

Marisela Noorhasan[1]; Daniel R. Drozd[1]; Aaron Blashill[2]; Greer Burkholder[3]; Karen Cropsey[3]; Matthew Mimiaga[2]; Katerina Christopoulos[4]; Carl Grunfeld[4]; **Heidi M. Crane**[1]
Centers for AIDS Research Network of Integrated Clinical Systems

[1]University of Washington, Seattle, WA, US; [2]Harvard Medical School, Boston, MA, US; [3]University of Alabama at Birmingham, Birmingham, AL, US; [4]University of California San Francisco, San Francisco, CA, US

Session P-Q12 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Complications: Liver Disease Without Viral Hepatitis

805 Antiretroviral Drugs Associated With Chronic ALT Elevations in Persons Without HCV and HBV Infection

Helen Kovari[1]; Caroline Sabin[2]; Bruno Ledergerber[1]; Lene Ryom[3]; Antonella d'Arminio Monforte[4]; Matthew G. Law[5]; Stéphane De Wit[6]; Andrew N. Phillips[2]; Jens D. Lundgren[3]; Rainer Weber[1]
on behalf of the D:A:D Study Group

[1]University Hospital Zurich, Zurich, Switzerland; [2]University College London, London, United Kingdom; [3]University of Copenhagen, Copenhagen, Denmark; [4]University of Milan, Milan, Italy; [5]University of New South Wales, Sydney, Australia; [6]St Pierre University Hospital, Brussels, Belgium

806 APRI and FIB4: Associated With D-Drug Exposure, Low CD4 Count and Monocyte Activation

Katherine W. Kooij[1]; Rosan van Zoest[1]; Ferdinand W. Wit[1]; Judith Schouten[2]; Neeltje Kootstra[2]; Ineke G. Stolte[3]; Maria Prins[3]; Peter Reiss[1]; Marc van der Valk[2]
AGEhIV Cohort Study Group

[1]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands; [2]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [3]Public Health Service of Amsterdam, Amsterdam, Netherlands

807 HIV and Liver Fibrosis Among Prison Inmates: The IeDEA West Africa Collaboration

Antoine Jaquet[1]; Gilles Wandeler[2]; Judicael Tine[3]; Claver Dagnra[4]; Alain Attia[5]; Akouda Patassi[6]; Abdoulaye Ndiaye[7]; Koumavi K. Ekouevi[8]; Moussa Seydi[3]; François Dabis[1]

[1]Inserm U897, ISPED, Université de Bordeaux, Bordeaux, France; [2]Department of Infectious Diseases, Bern University Hospital, Bern, Switzerland; [3]Service de Maladies Infectieuses et Tropicales, CRCF, CHU de Fann, Dakar, Senegal; [4]Service de Virologie, BIOLIM, Université de Lomé, Lomé, Togo; [5]Service de Hépato-Gastroentérologie, CHU de Yopougon, Abidjan, Côte d'Ivoire; [6]Service de Maladies Infectieuses et Tropicales, CHU Sylvanus Olympio, Lomé, Togo; [7]Service de Médecine Interne, CHU Aristide Le Dantec, Dakar, Senegal; [8]Département de Santé Publique, Faculté des Sciences de la Santé, Université de Lomé, Lomé, Togo

Session P-Q13 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Depression and Alcohol Use Disorders

808 Clinical Correlates of Alcohol Use Disorders Among HIV-Infected Adults in Zambia

Michael J. Vinikoor[1]; Masumba Masaninga[2]; Carolyn Bolton Moore[3]; Virginia Munamununungu[4]; Alice Siyunda[4]; Lloyd Mulenga[5]; Matthias Egger[6]; Benjamin H. Chi[3]; Gilles Wandeler[6]
IeDEA Southern Africa

[1]University of North Carolina, Lusaka, Zambia; [2]Lusaka District Health Management Team, Lusaka, Zambia; [3]University of North Carolina, Chapel Hill, NC, US; [4]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia; [5]University of Zambia, Lusaka, Zambia; [6]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

809 Depression and Treatment Outcomes Among Tanzanian Adults Initiating HAART

Christopher R. Sudfeld[1]; Sylvia Kaaya[2]; Nilupa S. Gunaratna[1]; Wafaie Fawzi[1]; Ferdinand Mugusi[2]; Mary C. Smith Fawzi[3]

[1]Harvard School of Public Health, Roxbury Crossing, MA, US; [2]Muhimbili University of Health and Allied Sciences, Dar es Salaam, United Republic of Tanzania; [3]Harvard Medical School, Boston, MA, US

TUESDAY, FEBRUARY 24, 2015

Session P-R1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Immune Reconstitution Inflammatory Syndrome in Opportunistic Infections

810 Discordant Early Immune Responses Distinguish TB IRIS and Death in HIV/TB Coinfection

Shruthi Ravimohan[1]; Neo Tamuhla[2]; Andrew Steenhoff[2]; Rona Letlhogile[2]; Kebatshabile Nfanyana[2]; Tumelo Rantleru[2]; Robert Gross[1]; Drew Weissman[1]; Gregory P. Bisson[1]

[1]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, US; [2]Botswana University of Pennsylvania Partnership, Gaborone, Botswana

811 WITHDRAWN

812 Exuberant Pathogen-Specific Th1 CD4+ T-Cell Responses in MAC-IRIS in HIV Infection

Kimberly F. Faldetta[1]; Denise C. Hsu[1]; Virginia Sheikh[1]; Gregg Roby[2]; Kenneth Olivier[1]; Irini Sereti[1]

[1]National Institutes of Health (NIH), Rockville, MD, US; [2]National Institutes of Health (NIH), Bethesda, MD, US

813 A Paradoxical Treatment of Mycobacterial Immune Reconstitution Inflammatory Syndrome

Denise C. Hsu; Kimberly F. Faldetta; **Luxin Pei**; Delmyra Turpin; Virginia Sheikh; Irini Sereti

National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

814 CD8 T Cells in Lesions of PML-IRIS Express CCR5: Rationale for the Use of Maraviroc

Guillaume Martin-Blondel[2]; Jan Bauer[1]; Emmanuelle Uro-Coste[2]; Hervé Dumas[2]; Hans Lassmann[1]; David Brassat[2]; Pierre Delobel; Roland Liblau[3]; Bruno Marchou[2]

[1]University of Vienna, Vienna, Austria; [2]Toulouse University Hospital, Toulouse, France; [3]Inserm, Toulouse, France

815 Monocyte Immune Responses in Cryptococcal Immune Reconstitution Inflammatory Syndrome

David B. Meya[1]; Godfrey Zziwa[2]; Samuel Okurut[2]; Stephen Cose[3]; Paul Bohjanen[4]; Sharon Wahl[5]; David R. Boulware[4]; Yuka Manabe[6]; Edward N. Janoff[7]

[1]Makerere University College of Health Sciences, Kampala, Uganda; [2]Makerere University Walter Reed Project, Kampala, Uganda; [3]Medical Research Council, Kampala, Uganda; [4]University of Minnesota, Minneapolis, MN, US; [5]National Institute for Dental and Craniofacial Research, Bethesda, MD, US; [6]Johns Hopkins University School of Medicine, Baltimore, MD, US; [7]University of Colorado, Denver, CO, US

816LB Does HIV Infection Reduce the Probability of Transmission of Pulmonary Tuberculosis?

Judith R. Glynn[1]; José Afonso Guerra-Assunção[1]; Rein M. Houben[1]; Themba Mzembe[2]; Lifted Sichali[2]; Palwasha Y. Khan[1]; Ruth McNerney[1]; Julian Parkhill[3]; Taane G. Clark[1]; Amelia C. Crampin[1]

[1]London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]Karonga Prevention Study, Chilumba, Malawi; [3]Wellcome Trust Sanger Institute, Hinxton, United Kingdom

Session P-R2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

T-Cell Responses to Tuberculosis Infection

817 The Relationship Between T-Regulatory Cells and Latent Tuberculosis Infection in Household Contacts Exposed to Pulmonary Tuberculosis Infection in Kampala, Uganda

Rhoda Namakula[1]; Irene A. Odanga[2]; Josephine Kasolo[2]; Ekii A. Abuku[3]

[1]Makerere University–Johns Hopkins Research Collaboration, Kampala, Uganda; [2]Makerere University College of Health Sciences, Kampala, Uganda; [3]Medical Research Council (Uganda Virus Research Institute), Entebbe, Uganda

818 Antiretroviral Therapy Fails to Restore Mycobacterium Tuberculosis-specific Th1 and Th17 CD4 Responses

Lyle W. Murray[1]; Dominique Goedhals[2]; Iman Satti[1]; Rodney Phillips[1]; Helen McShane[1]; John Frater[1]
Phillips/Frater

[1]University of Oxford, Oxford, United Kingdom; [2]University of the Free State, Bloemfontein, South Africa

819 Treg/Th17 and T-Cell Effector Responses in Tuberculosis Patients Coinfected with HIV

Christine Lacabaratz[1]; Aurelie Wiedemann[1]; Celine Manier[1]; Laure Bourdery[1]; Mathieu Surenaud[1]; Jean-Daniel Lelièvre[2]; Giovanna Melica[3]; Yves Lévy[2]

[1]INSERM U955, Université Paris-Est Créteil, Vaccine Research Institute, Créteil, France; [2]INSERM U955, Université Paris-Est Créteil, Vaccine Research Institute, CHU H. Mondor-A.Chenevier, Créteil, France; [3]CHU H. Mondor-A.Chenevier, Créteil, France

820 HIV-Tuberculosis Coinfection Leads to Increased Turnover of Late-Senescent CD8$^+$ T Cells

Shankar Esaki Muthu[1]; Chong Yee Kien[1]; Alireza Saeidi[1]; Adeeba Kamarulzaman[1]; Vijayakumar Velu[2]; Marie Larsson[3]

[1]University of Malaya, Kuala Lumpur, Malaysia; [2]Emory University, Atlanta, GA, US; [3]Linkoping University, Linkoping, Sweden

821 CD8 T-Cell Terminal Differentiation and Its Regulation by DHEA in HIV-TB Coinfection

Guadalupe V. Suarez[1]; Matias T. Angerami[1]; Maria B. Vecchione[1]; Omar Sued[2]; Horacio Salomon[1]; Maria F. Quiroga[1]

[1]INBIRS (UBA-CONICET), Buenos Aires, Argentina; [2]Fundacion Huesped, Buenos Aires, Argentina

Session P-R3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

TB Diagnostic Challenges

822 Unsuspected Prevalent TB among HIV-Infected Pregnant Women, South Africa

Jennifer D. Hoffmann[1]; **Silvia E. Cohn**[1]; Fildah Mashabela[2]; Ziyaad Waja[2]; Christopher J. Hoffmann[1]; Neil Martinson[2]; Richard E. Chaisson[1]
Tshepiso Study Team

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Perinatal HIV Research Unit (PHRU), Johannesburg, South Africa

823 Evaluation of WHO 4-Symptom Tool to Rule Out TB: Data From the XPHACTOR Study

Yasmeen Hanifa[1]; Katherine Fielding[1]; Violet Chihota[2]; Nontobeko Ndlovu[2]; Alan Karstaedt[3]; Lungiswa Adonis[4]; Linda Erasmus[5]; Mark Nicol[5]; Gavin Churchyard[2]; Alison Grant[1]

[1]London School of Hygiene & Tropical Medicine, London, United Kingdom; [2]Aurum Institute for Health Research, Johannesburg, South Africa; [3]Chris Hani Baragwanath Hospital, Johannesburg, South Africa; [4]Mamelodi Hospital, Pretoria, South Africa; [5]National Health Laboratory Service, Johannesburg, South Africa

824 Xpert MTB/RIF Versus AFB Smear to Determine Respiratory Isolation of US TB Suspects

Anne Luetkemeyer[1]; Cynthia Firnhaber[7]; Michelle Kendall[2]; Xingye Wu[2]; Debra Benator[3]; Gerald Mazurek[4]; Diane Havlir[1]; Beatriz Grinsztejn[5]; David Alland[6]
on behalf of the ACTG A5295/TBTC 34 Study Teams

[1]San Francisco General Hospital, University of California San Francisco, San Francisco, CA, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]Washington DC Veterans Affairs Medical Center, Washington, DC, US; [4]US Centers for Disease Control and Prevention, Atlanta, GA, US; [5]Instituto de Pesquisa Clinica Evandro Chagas, Rio de Janiero, Brazil; [6]Rutgers New Jersey Medical School, Newark, NJ, US; [7]University of Witswatersrand, Johannesburg, South Africa; [8]ACTG A5295/TBTC 34 Study Teams, N/a, MA, US

825 Needle Autopsies Highlight Challenges in Defining HIV+ TB Deaths Using Verbal Autopsy

Aaron Karat[1]; Mpho Tlali[2]; Salome Charalambous[2]; Kerrigan McCarthy[2]; Violet Chihota[2]; Gavin Churchyard[2]; Katherine Fielding[1]; Kathleen Kahn[3]; Tanvier Omar[4]; Alison Grant[1]

[1]London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]The Aurum Institute, Johannesburg, South Africa; [3]University of the Witwatersrand, Johannesburg, South Africa; [4]National Health Laboratory Service, Wits School of Public Health, Johannesburg, South Africa

826 Delta-Like 1 Protein, Vitamin D Binding Protein, and Fetuin Measurement in Cerebrospinal Fluid for Detection of *Mycobacterium tuberculosis* Meningitis

Nathan C. Bahr[1]; Ryan Halupnick; Grace Linder; Reuben Kiggundu[2]; Henry W. Nabeta[2]; Darlisha Williams[1]; Srinand Srevatsan[3]; Joshua Rhein[1]; David B. Meya[2]; David R. Boulware[1]

[1]University of Minnesota, Minneapolis, MN, US; [2]Makerere University College of Health Sciences, Kampala, Uganda; [3]University of Minnesota, Minneapolis, MN, US

827LB Adherence to Once-Weekly Self-Administered INH and Rifapentine for Latent TB: iAdhere

Robert Belknap[1]; Andrey Borisov[2]; David Holland[3]; Pei-Jean Feng[2]; Joan-Pau Millet[4]; Neil Martinson[5]; Alicia Wright[6]; Michael Chen[2]; Joan Cayla[4]; Jose M. Mida[7]
and the Tuberculosis Trials Consortium (TBTC)

[1]Denver Health and Hospital Authority, Denver, CO, US; [2]US Centers for Disease Control and Prevention, Altanta, GA, US; [3]Emory University, Atlanta, GA, US; [4]Tuberculosis Investigation Unit of Barcelona, Barcelona, Spain; [5]University of Witwatersrand, Johannesburg, South Africa; [6]Vanderbilt University, Nashville, TN, US; [7]Hospital Clinic–IDIBAPS, University of Barcelona, Barcelona, Spain

828LB Wirelessly Observed Therapy (WOT): A New Paradigm in TB Therapy Monitoring

Sara Browne[1]; Richard Haubrich[1]; Kathleen S. Moser[2]; Lorenzo DiCarlo[3]; Charles A. Peloquin[4]; Constance A. Benson[1]

[1]University of California San Diego, San Diego, CA, US; [2]San Diego County Health and Human Services Agency, San Diego, CA, US; [3]Proteus Digital Health Inc, Redwood City, CA, US; [4]University of Florida College of Pharmacy, Gainesville, FL, US

Session P-R4 Poster Session — Poster Hall

2:30 pm – 4:00 pm

TB Adverse Events, Recurrence, and Mortality

829 Severe Adverse Events in Outpatient Drug-Resistant TB Treatment in South Africa

Rebecca H. Berhanu[1]; Kathryn Schnippel[2]; Andrew Black[3]; Erika Mohr[4]; Busi Mncube[1]; Ian Sanne[1]

[1]Health Economics and Epidemiology Research Organisation, Johannesburg, South Africa; [2]Right to Care, Johannesburg, South Africa; [3]Reproductive Health Institute, University of Witswatersrand, Johannesburg, South Africa; [4]Médecins Sans Frontières, Cape Town, South Africa

830 Decreased TB Recurrence After Introduction of ART in Durban, South Africa

Yuri F. van der Heijden[1]; Farina Karim[2]; Gary Parker[2]; Tilagavathy Chinappa[3]; Grace Mufamadi[3]; Linda Zako[3]; Bryan E. Shepherd[1]; Timothy Sterling[1]; Alexander Pym[2]

[1]Vanderbilt University, Nashville, TN, US; [2]KwaZulu Natal Research Institute for TB and HIV (K-RITH), Durban, South Africa; [3]Ethekwini Municipality, Durban, South Africa

831 Incidence of Active Tuberculosis in HIV-Infected Adults and Mortality in Thailand

Nicolas Salvadori[1]; Suwalai Chalermpantmetagul[1]; Julie Figoni[1]; Suchart Thongpaen[2]; Ampaipith Nilmanat[3]; Patinun Chirawatthanaphan[4]; Pramual Thaingamsilp[5]; Tim R. Cressey[1]; Nicole Ngo-Giang-Huong[1]; Gonzague Jourdain[1]

[1]Institut de Recherche Pour le Développement UMI 174-PHPT, Chiang Mai, Thailand; [2]Mahasarakham Hospital, Mahasarakham, Thailand; [3]Hat Yai Hospital, Hat Yai, Thailand; [4]Phaholpolpayuhasaena Hospital, Kanchanaburi, Thailand; [5]Kalasin Hospital, Kalasin, Thailand

832 Antiretroviral Scale-up and Tuberculosis Mortality in High-Burden Countries

Eline Korenromp[2]; **Eran Bendavid**[1]; Isabel Yan[1]

[1]Stanford University, Stanford, CA, US; [2]Futures Institute, Glastonbury, CT, US

833 Culture-Negative TB Is Associated With Increased Mortality in HIV-Infected Persons

Timothy Sterling[1]; Cathy Jenkins[1]; Karu Jayathilake[1]; Eduardo Gotuzzo[2]; Valdilea Veloso[3]; Claudia P. Cortes[4]; Denis Padgett[5]; Brenda Crabtree-Ramirez[6]; Bryan E. Shepherd[1]; Catherine McGowan[1]
CCASAnet

[1]Vanderbilt University, Nashville, TN, US; [2]Universidad Peruana Cayetano Heredia, Lima, Peru; [3]Instituto Pequisa Evandro Chagas, Rio de Janeiro, Brazil; [4]University of Chile, Santiago, Chile; [5]Instituto Hondureno de Seguruidad Social, Tegucigalpa, Honduras; [6]Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico

THURSDAY, FEBRUARY 26, 2015

Session P-R5 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Cryptococcal Meningitis: Host Response, Treatment, and Outcomes

834 Local and Systemic Humoral Responses to Cryptococcal Meningitis in Patients With AIDS

Erin E. Finn[1]; Jordan Janoff[1]; Jeremy Rahkola[1]; David B. Meya[2]; Samuel Okurut[2]; Andrew D. Kambugu[2]; Paul Bohjanen[3]; Kirsten Nielsen[3]; David R. Boulware[3]; Edward N. Janoff[1]

[1]Mucosal and Vaccine Research Colorado, Aurora, CO, US; [2]Makerere University College of Health Sciences, Kampala, Uganda; [3]University of Minnesota, Minneapolis, MN, US

835 Antiretroviral Therapy Alters the CSF Immune Response in Cryptococcal Meningitis

James E. Scriven[1]; Britta Urban[1]; Lisa Graham[2]; Charlotte Schutz[2]; Robert J. Wilkinson[3]; David R. Boulware[4]; David Lalloo[1]; Graeme Meintjes[2]

[1]Liverpool School of Tropical Medicine, Liverpool, United Kingdom; [2]University of Cape Town, Cape Town, South Africa; [3]Imperial College London, London, United Kingdom; [4]University of Minnesota, Minneapolis, MN, US

836 Detrimental Outcomes of Unmasking Cryptococcal Meningitis With Recent ART Initiation

Joshua Rhein[1]; Katherine H. Hullsiek[1]; Nathan C. Bahr[1]; Reuben Kiggundu[3]; Darlisha Williams[3]; Henry W. Nabeta[3]; Abdu Musubire[3]; David B. Meya[3]; David R. Boulware[1]

[1]University of Minnesota, Minneapolis, MN, US; [2]University of Minnesota, Minneapolis, MN, US; [3]Makerere University College of Health Sciences, Kampala, Uganda

837 Impact of ART on Mortality in Cryptococcal Meningitis Patients: High-Income Settings

Suzanne M. Ingle[1]; Jose M. Miro[2]; Hansjakob Furrer[4]; Amy Justice[5]; Michael S. Saag[6]; Christian Manzardo[2]; Anna Esteve[7]; Lauren E. Cain[3]; Jonathan A. Sterne[1]; Margaret T. May[1]

[1]University of Bristol, Bristol, United Kingdom; [2]Hospital Clínic–L'Institut D'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain; [3]Harvard School of Public Health, Boston, MA, US; [4]Bern University Hospital and University of Bern, Bern, Switzerland; [5]Yale University School of Medicine, VA Connecticut Healthcare System, New Haven, CT, US; [6]University of Alabama at Birmingham, Birmingham, AL, US; [7]Centre d'Estudis Epidemiològics Sobre ITS/VIH/SIDA de Catalunya, Barcelona, Spain

838 Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis

Joshua Rhein[1]; Katherine H. Hullsiek[1]; Bozena Morawski[1]; Kyle Smith[1]; Ali Al-Hadab[1]; Abdu Musubire[2]; Darlisha Williams[2]; Kristen Nielsen[1]; David B. Meya[2]; David R. Boulware[1]

[1]University of Minnesota, Minneapolis, MN, US; [2]Makerere University College of Health Sciences, Kampala, Uganda

TUESDAY, FEBRUARY 24, 2015

Session P-R6 Poster Session — **Poster Hall**

2:30 pm – 4:00 pm

Syphilis and HIV Coinfection

839 Infection With HIV Among Individuals With Primary and Secondary Syphilis: USA, 2013

John R. Su; Akbar A. Zaidi; Elizabeth A. Torrone; Hillard S. Weinstock

US Centers for Disease Control and Prevention, Atlanta, GA, US

840 Risk Factors for Asymptomatic and Symptomatic Neurosyphilis Differ in HIV-Infected Patients With Syphilis

Christina Marra; Trudy Jones; Shelia Dunaway; Emily Ho; Abigail Crooks; Lauren Tantalo; Sharon Sahi

University of Washington, Seattle, WA, US

841 High Incidence of Syphilis Among Thai MSM Who Started ART Therapy During Acute HIV Infection

Donn J. Colby[1]; Suteeraporn Pinyakorn[1]; Frits van Griensven[1]; Eugene Kroon[1]; Naphassanant Laopraynak[1]; Robert O'Connell[2]; Nelson L. Michael[2]; Praphan Phanuphak[1]; Jintanat Ananworanich[2]; Nittaya Phanuphak[1]

[1]Thai Red Cross AIDS Research Center, Bangkok, Thailand; [2]US Military HIV Research Program, Bethesda, MD, US

842 Serological Response to Treatment of Syphilis in HIV-Positive and HIV-Negative Adults

Rulin C. Hechter[1]; Robyn Neblett Fanfair[2]; W-L Joanie Chung[1]; Lauri E. Markowitz[2]; Sean S. Anand[1]

[1]Kaiser Permanente Southern California, Pasadena, CA, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Session P-R7 Poster Session — **Poster Hall**

2:30 pm – 4:00 pm

Opportunistic Infections: Odds and End Organs

843 The Exposure and Geospatial Risk Factors for AIDS-Associated Penicilliosis in Vietnam

Thuy Le[1]; Brian Jonat[2]; Ngo T. Cuc[3]; Nguyen T. Thanh[1]; Dang T. Bich[4]; Cecilia Shikuma[5]; Jeremy Day[1]; Heiman Wertheim[1]; Jeremy Farrar[1]; Marcel Wolbers[1]

[1]Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam; [2]New York-Presbyterian University Hospital of Columbia and Cornell, New York City, NY, US; [3]Hospital for Tropical Diseases, Ho Chi Minh City, Viet Nam; [4]National Hospital for Tropical Diseases, Hanoi, Viet Nam; [5]Hawaii Center for AIDS, University of Hawaii, Ho Chi Minh, Viet Nam

844 A5265 Clinical Trial: Gentian Violet for Oral Candidiasis is as Effective as Nystatin

Pranab K. Mukherjee[1]; Lauren Patton[2]; James Hakim[4]; Huichao Chen[3]; Mai T. Pho[5]; Kenneth A. Freedberg[6]; Caroline Shiboski[7]; Mahmoud A. Ghannoum[1]; Robert A. Salata[1]
Oral HIV/AIDS Research Alliance (OHARA)/ACTG

[1]Case Western Reserve University, Cleveland, OH, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]Harvard School of Public Health, Boston, MA, US; [4]University of Zimbabwe - Parirenyatwa, Harare, Zimbabwe; [5]University of Chicago, Chiago, IL, US; [6]Harvard Medical School, Boston, MA, US; [7]University of California San Francisco (UCSF), San Francisco, CA, US

845 Effective Treatment of Lymphogranuloma Venereum (LGV) With 1g Azithromycin Administered Weekly for 3 Weeks in an HIV-Infected Population

José L. Blanco; Irene Fuertes; Jordi Bosch; Ana Gonzalez; Andrea Vergara; Rob Camp; Esteban Martinez; Teresa Estrach; Josep M. Gatell; Merçe Alsina

Hospital Clinic, Barcelona, Barcelona, Spain

846 Risk Factors for Staphylococcus Aureus Carriage in HIV-Infected Adults in Southern Botswana

Michael J. Reid[1]; **Rebceca Fischer**[3]; Naledi Mannathoko[2]; Eric Brown[3]; Andrew Steenhoff[4]

[1]University of California San Francisco, San Francisco, CA, US; [2]University of Botswana, School of Medicine, Gaborone, Botswana; [3]University of Texas, Texas, Afghanistan; [4]University of Pennsylvania, Gaborone, Botswana

847 Specific Behaviors Predict *Staphylococcus aureus* Colonization and Skin and Soft Tissue Infections Among HIV-Infected Persons

Nancy Crum-Cianflone; Xun Wang; Amy Weintrob; Tahaniyat Lalani; Mary Bavaro; Katrin Mende; Michael Ellis; Brian K. Agan

Infectious Disease Clinical Research Program, San Diego, CA, US

848 Cytokine Profile in Aqueous Humor of HIV Patients With Ocular Opportunistic Infections

Matilde Ruiz-Cruz; Santiago Avila-Rios; Christopher Ormsby; Claudia Alvarado-de la Barrera; Yuria Ablanedo-Terrazas; Gustavo Reyes-Terán

National Institute of Respiratory Diseases, Mexico City, Mexico

849 Effects of *H. pylori* Co-infection on Immune Parameters in HIV-1 Patients in Ghana

Edmund Osei-Kuffour[1]; Torsten Feldt[1]; Kirsten A. Eberhardt[2]; Fred S. Sarfo[4]; Marieke Soltau[2]; Jan F. Drexler[3]; Gerd D. Burchard[2]; Carsten Münk[1]; Dieter Häussinger[1]
HHECO Study Group

[1]University Clinic Düsseldorf, Heinrich-Heine-University, Düsseldorf, Germany; [2]Bernhard-Nocht-Institute for Tropical Medicine, Hamburg, Hamburg, Germany; [3]University of Bonn, Bonn, Germany; [4]Kwame Nkrumah University of Science and Technology, Komfo Anokye Teaching Hospital, Kumasi, Ghana

THURSDAY, FEBRUARY 26, 2015

Session P-S1 Poster Session — **Poster Hall**

2:30 pm – 4:00 pm

Access and Engagement

850 Trends in Healthcare Access and HIV Risk Behaviors—African American Women, 2006-2013

Wade Ivy; Gabriela Paz-Bailey

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

851 Engagement in the HIV Care Continuum Among Female Sex Workers in Lilongwe, Malawi

Kathryn E. Lancaster[1]; Thandie Lungu[3]; Mina C. Hosseinipour[3]; Katy Chadwick[2]; Zoe Dibb[2]; Vivian F. Go[1]; Brian W. Pence[1]; Kimberly A. Powers[1]; Irving F. Hoffman[1]; William C. Miller[1]

[1]University of North Carolina, Chapel Hill, NC, US; [2]Theatre for a Change, Lilongwe, Malawi; [3]University of North Carolina Project–Malawi, Lilongwe, Malawi

852 New HIV Cases and ARV Retention in Pretoria: A Gender Project for High-Risk Women

Wendee M. Wechsberg[1]; William A. Zule[1]; Irene A. Doherty[1]; Tracy L. Kline[1]; Jacqueline Ndirangu[1]; Charles M. van der Horst[2]

[1]RTI International, Research Triangle Park, NC, US; [2]University of North Carolina, Chapel Hill, NC, US

853 Intimate Partner Violence and Antiretroviral Adherence in HIV-Positive Women in Kenya

Kate S. Wilson[1]; Krista Yuhas[1]; Ruth Deya[1]; Barbra Richardson[1]; Linnet Masese[1]; Jane Simoni[1]; Walter Jaoko[2]; R Scott McClelland[1]

[1]University of Washington, Seattle, WA, US; [2]University of Nairobi, Nairobi, Kenya

854 Re-engagement in Care Leads to Sustained Engagement and Viral Suppression

Brittani D. Saafir-Callaway[1]; Amanda D. Castel[2]; Lena Lago[1]; Christie Olejemeh[1]; Garret Lum[1]; Lawrence Frison[1]; Michael Kharfen[1]

[1]District of Columbia Department of Health, Washington, DC, US; [2]The Milken Institute School of Public Health at George Washington University, Washington, DC, US

TUESDAY, FEBRUARY 24, 2015

Session P-S2 Poster Session — **Poster Hall**

2:30 pm – 4:00 pm

Cervical Sampling, Shedding, and Outcomes

855 Symptoms and Genital HSV-2 and HIV-1 in Coinfected Women, Chiang Rai, Thailand

Eileen F. Dunne[1]; Brooke E. Hoots[1]; Janet McNicholl[1]; Sara Whitehead[2]; Thomas A. Peterman[2]; Lauri E. Markowitz[2]; Wanna Leelawiwat[3]; Tammy Evans-Strickfaden[1]; Cheng Chen[1]

[1]US Centers for Disease Control and Prevention, Bangkok, Thailand; [2]US Centers for Disease Control and Prevention, Atlanta, GA, US; [3]Thailand Ministry of Public Health–US CDC Collaboration, Nonthaburi, Thailand

856 High-Risk HPV Clustering and Cervical Outcomes in HIV-Infected Women in Rio de Janeiro, Brazil

Jessica L. Castilho[1]; José Eduardo Levi[2]; Paula M. Luz[2]; Mary Catherine Cambou[3]; Tazio Vanni[4]; Angela de Andrade[2]; Monica Derrico[2]; Valdilea Veloso[2]; Beatriz Grinsztejn[2]; Ruth Friedman[2]

[1]Vanderbilt University School of Medicine, Nashville, TN, US; [2]Fundação Oswaldo Cruz, Rio de Janeiro, Brazil; [3]University of California Los Angeles, Los Angeles, CA, US; [4]United Nations, Lyons, France

857 Comparison of Three Female Genital Tract Sampling Techniques for HIV RNA Recovery

Catherine S. Todd[1]; Shameem Jaumdally[2]; Heidi E. Jones[3]; Hoyam Gamieldien[2]; Nontokozo Langwenya[4]; Landon Myer[4]; Donald R. Hoover[5]; Jo-Ann Passmore[1]

[1]FHI360, Bangkok, Thailand; [2]University of Cape Town, Cape Town, South Africa; [3]Hunter College, CUNY School of Public Health, New York, NY, US; [4]University of Cape Town, Cape Town, South Africa; [5]Rutgers New Jersey Medical School, Piscataway, NJ, US

THURSDAY, FEBRUARY 26, 2015

Session P-S3 Poster Session — **Poster Hall**

2:30 pm – 4:00 pm

Hormonal Contraception

858 CCR5 Expression in HIV-Uninfected Women Receiving Hormonal Contraception

Athe Tsibris[1]; Gaia Sciaranghella[2]; Cuiwei Wang[3]; Kerry Murphy[4]; Zaher Mehri[5]; Ruth M. Greenblatt[6]; Mardge Cohen[7]; Elizabeth Golub[8]; Heather Watts[9]; Mary A. Young[3]

[1]Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, US; [2]Ragon Institute of MIT, MGH and Harvard, Boston, MA, US; [3]Georgetown University Medical Center, Washington, DC, US; [4]Albert Einstein College of Medicine, Bronx, NY, US; [5]University of Vermont College of Medicine, Burlington, VT, US; [6]University of California San Francisco, San Francisco, CA, US; [7]Stroger Hospital and Rush University and CORE Center, Chicago, IL, US; [8]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [9]The Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US

859 Estrogen Replacement in Healthy Postmenopausal Women Reduces %CCR5+ CD4+ T Cells

Amie Meditz[1]; Samantha MaWhinney[2]; Kerrie Moreau[2]; Kelsey Melander[2]; Joy Folkvord[2]; Wendy Kohrt[2]; Margaret Wierman[2]; Elizabeth Connick[2]

[1]Boulder Community Health, Boulder, CO, US; [2]University of Colorado Anschutz Medical Campus, Aurora, CO, US

860 Progesterone Increases Are Associated With HIV Susceptibility Factors in Women

Alison Y. Swaims[1]; Tammy Evans-Strickfaden[1]; L Davis Lupo[1]; Alfredo Aguirre[2]; Anandi Sheth[2]; Igho Ofotokun[2]; Clyde E. Hart[1]; **Richard E. Haaland**[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]Emory University School of Medicine, Atlanta, GA, US

861 Changes in Vaginal Microbiota and Cytokines in HIV-1-Seronegative Women Initiating DMPA

Alison C. Roxby[1]; David N. Fredricks[2]; Katherine Odem-Davis[1]; Kristjana H. Ásbjörnsdóttir[1]; Linnet Masese[1]; Tina L. Fiedler[2]; Walter Jaoko[3]; James N. Kiarie[3]; Julie M. Overbaugh[2]; R Scott McClelland[1]

[1]University of Washington, Seattle, WA, US; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [3]University of Nairobi, Nairobi, Kenya

862 A Thinned Vaginal Stratum Corneum Is a Susceptibility Factor for SHIV Acquisition

Ellen Kersh; Jana Ritter; Katherine Butler; Sharon Dietz Ostergaard; Debra Hanson; Sherif Zaki; Janet McNicholl

US Centers for Disease Control and Prevention, Atlanta, GA, US

TUESDAY, FEBRUARY 24, 2015

Session P-T1 Poster Session — **Poster Hall**

2:30 pm – 4:00 pm

How Fast? How Often? Achieving Viral Suppression in Pregnant and Postpartum Women

863 Specific Effects of ZDV, 3TC and LPV/r on HIV-1 RNA Viral Load During Pregnancy

Patumrat Sripan[1]; Sophie Le Coeur[5]; Lily Ingsrisawang[2]; Tim R. Cressey[3]; Jean-Marc Tréluyer[6]; Naïm Bouazza[4]; Frantz Foissac[4]; Gonzague Jourdain[3]; Marc G. Lallemant[3]; Saïk Urien[7]

[1]ED420, University of Paris Sud 11, Paris Descartes, Paris, France/PHPT-IRD UMI 174, Chiang Mai, Thailand/Department of Statistics, Faculty of Science, Kasetsart University, Bangkok, Thailand; [2]Department of Statistics, Faculty of Science, Kasetsart University, Bangkok, Thailand; [3]PHPT-IRD UMI 174, Faculty of Associated Medical Sciences, Chiang Mai University/ Harvard School of Public Health, Chiang Mai, Thailand; [4]EA 08 Université Paris Descartes, Sorbonne Paris Cité, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, Paris, France; [5]Institut d'Etudes Démographiques, Institut de Recherche Pour le Développement (UMR 196 CEPED), Paris, France/Harvard School of Public Health, Boston, MA, USA/Faculty of Associated Medical Science, Chiang Mai University, Chiang Mai, Thailand; [6]EA 08 Université Paris Descartes, Sorbonne Paris Cité, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, Service de Pharmacologie Clinique, AP-HP, Groupe Hospitalier Paris Centre, CIC-0901 Inserm, Cochin-Necker, Paris, France; [7]EA 08 Université Paris Descartes, Sorbonne Paris Cité, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, CIC-0901 Inserm, Cochin-Necker, Paris, France

864 Viral Suppression After Antiretroviral Therapy Initiation in Pregnancy in South Africa

Landon Myer[1]; Tamsin Phillips[1]; Nei-Yuan Hsiao[2]; Allison Zerbe[3]; Jo Ramjith[1]; Linda-Gail Bekker[1]; James A. McIntyre[4]; Elaine J. Abrams[3]

[1]University of Cape Town, Cape Town, South Africa; [2]National Health Laboratory Services/ University of Cape Town, Cape Town, South Africa; [3]ICAP at Columbia University, New York, NY, US; [4]Anova Health Institute, Johannesburg, South Africa

865 Maternal Viral Load in the Context of PMTCT B+ Within the Kabeho Study in Kigali

Emily A. Bobrow[1]; Placidie Mugwaneza[2]; Gilles F. Ndayisaba[3]; Dieudonne Ndatimana[3]; **Michelle Gill**[1]; Heather J. Hoffman[4]; Cyprien Baribwira[5]; Laura Guay[1]; Anita Asiimwe[6]
Kabeho Study Team

[1]Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, US; [2]Ministry of Health, Kigali, Rwanda; [3]Elizabeth Glaser Pediatric AIDS Foundation, Kigali, Rwanda; [4]George Washington University Milken Institute School of Public Health, Washington, DC, US; [5]University of Maryland, School of Medicine, Kigali, Rwanda; [6]Rwanda University Teaching Hospitals, Kigali, Rwanda

866 ART Response Among Pregnant and Postpartum Women With Acute Versus Chronic HIV-1

Alison L. Drake[1]; John Kinuthia[2]; Daniel Matemo[2]; Barbra Richardson[1]; Michael Chung[1]; James N. Kiarie[2]; Sandy Emery[3]; Julie M. Overbaugh[3]; Grace John-Stewart[1]

[1]University of Washington, Seattle, WA, US; [2]University of Nairobi, Nairobi, Kenya; [3]Fred Hutchinson Cancer Research Center, Seattle, WA, US

Session P-T2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Rates and Risks of MTCT and HIV-Free Survival

867 No Perinatal Transmission of HIV-1 in Women Efficiently Treated Since Conception

Laurent Mandelbrot[1]; Roland Tubiana[2]; Jérome Le Chenadec[3]; Catherine Dollfus[4]; Albert Faye[5]; Christine Rouzioux[6]; Anais Perilhou[3]; **Josiane Warszawski**[7]; Stéphane Blanche[6]
The ANRS-EPF (CO1/CO10/CO11) Study Group

[1]AP-HP, Hôpital Louis Mourier - INSERM U1018, CESP - Université Paris 7, Colombes, France; [2]AP-HP, Hôpital Pitié Salpêtrière - INSERM, U943, Paris, France; [3]INSERM CESP U1018, Le Kremlin-Bicetre, France; [4]AP-HP, Hôpital Trousseau, Paris, France; [5]AP-HP, Hôpital Robert Debre-University Paris 7, Paris, France; [6]AP-HP, Hôpital Necker-Enfants Malades, University Paris-Descartes, Paris, France; [7]University Paris-Sud - INSERM CESP U1018 - AP-HP Hopital Bicetre, Le Kremlin-Bicetre, France

868 Predictors of Perinatal HIV Transmission in the BAN Study

Sascha R. Ellington[1]; **Athena P. Kourtis**[1]; Ali Fokar[2]; Charles S. Chasela[4]; Dumbani Kayira[3]; Gerald Tegha[3]; Denise J. Jamieson[1]; Charles M. van der Horst[2]
The BAN Study Team

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]University of North Carolina Project Lilongwe, Lilongwe, Malawi; [4]University of Witwatersrand, Johannesburg, South Africa

869 High Rate of HIV Superinfection After Delivery: Secondary Analysis of the PEPI Trial

Andrew D. Redd[1]; Sarah Wendel[1]; Andrew Longosz[1]; Jessica M. Fogel[2]; Newton Kumwenda[3]; Sufia Dadabhai[3]; Susan H. Eshleman[2]; Stephen Porcella[4]; Thomas C. Quinn[1]; Taha Taha[3]

[1]National Institute of Allergy and Infectious Diseases, Baltimore, MD, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [4]National Institute of Allergy and Infectious Diseases (NIAID), Hamilton, MT, US

870 Decline in Early Mother-to-Child HIV Transmission (MTCT) Risk Over Time in Botswana

Kathleen M. Powis[1]; Gbolahan Ajibola[2]; Jean Leidner[3]; Kara Bennett[4]; Florence Chilisa[2]; Keabetwe Bedi[2]; Chipo Petlo[7]; Michael D. Hughes[8]; Roger Shapiro[5]; Shahin Lockman[6]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]Botswana Harvard AIDS Institute, Gaborone, Botswana; [3]Goodtables Data Consulting, Norman, OK, US; [4]Bennett Statistical Consulting, Inc, Ballston Lake, NY, US; [5]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US; [6]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [7]Botswana Ministry of Health, Gaborone, Botswana; [8]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US

871 Impact of Maternal Antiretroviral Regimen on Six-Month HIV-Free Survival in Botswana

Rebecca Zash[1]; Sajini Souda[2]; Chazha Hick[3]; Kelebogile Binda[3]; Sikhulile Moyo[3]; Erik van Widenfeldt[3]; Jean Leidner[4]; Joseph Makhema[3]; Mompati Mmalane[3]; Roger Shapiro[1]

[1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US; [2]University of Botswana, Gaborone, Botswana; [3]Botswana Harvard AIDS Institute, Gaborone, Botswana; [4]Harvard School of Public Health, Boston, MA, US

872 Infant Outcomes Among a Cohort of HIV-Infected Pregnant Women With and Without TB in South Africa: The Tshepiso Study

Jennifer D. Hoffmann[1]; Silvia E. Cohn[1]; **Nicole M. Salazar-Austin**[1]; Fildah Mashabela[2]; Ziyaad Waja[2]; Christopher J. Hoffmann[1]; Sanjay Lala[3]; Richard E. Chaisson[1]; Neil A. Martinson[2]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Perinatal HIV Research Unit (PHRU), Johannesburg, South Africa; [3]Chris Hani Baragwanath Hospital, Johannesburg, South Africa

Session P-T3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Option B+: Retention and Transmission

873 Early HIV Infection Rate Trends in Exposed Infants Pre- and Post-Option B+ in Mozambique

Thresia Sebastian; Serena Brusamento; Laurence Ahoua; Dario Aly; Stephen M. Arpadi; Chloe A. Teasdale; Fatima Tsiouris; Elaine J. Abrams

ICAP at Columbia University, New York, NY, US

874 Option B+ Scale Up and Comprehensive PMTCT Service Delivery in Central Malawi

Michael E. Herce[1]; Tiwonge Mtande[2]; Frank Chimbwandira[3]; Innocent Mofolo[2]; Christine Chingondole[2]; Nora Rosenberg[4]; Kathryn Lancaster[4]; Mina C. Hosseinipour[1]; Charles M. van der Horst[1]
Safeguard the Family—Malawi Ministry of Health Partnership

[1]University of North Carolina, Lusaka, Zambia; [2]UNC Project-Malawi, Lilongwe, Malawi; [3]Malawi Ministry of Health, Lilongwe, Malawi; [4]University of North Carolina, Chapel Hill, NC, US

875 Retention Amongst HIV-Infected Pregnant Women Initiating Lifelong Antiretroviral Treatment (Option B+) in Haiti

Jean W. Domercant[2]; Nancy Puttkammer[3]; **Lydia Lu**[1]; Kesner Francois[4]; Olbeg Desinor[5]; Reginald Jean_Louis[2]; Michelle Adler[1]; Barbara Marston[1]; Reynold Grand'Pierre[4]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]US Centers for Disease Control and Prevention (CDC), Port au Prince, Haiti; [3]International Training and Education Center for Health, Seattle, WA, US; [4]Ministry of Health of the Government of Haiti, Port au Prince, Haiti; [5]US Agency for International Development, Port au Prince, Haiti

THURSDAY, FEBRUARY 26, 2015

Session P-T4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Health Outcomes of HIV- and ARV-Exposed Infants, Children, and Youth

876 Malnutrition Among HIV-Exposed Uninfected Children in Botswana

Kathleen M. Powis[1]; Quanhong Lei[2]; Yvonne Chinyanga[3]; Esther Tumbare[4]; Nealia Khan[5]; Jacinta Sibiya[3]; Erik van Widenfelt[6]; Joseph Makhema[6]; Roger Shapiro[7]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]Botswana Ministry of Health, Gaborone, Botswana; [4]Elizabeth Glaser Pediatric AIDS Foundation, Harare, Zimbabwe; [5]Harvard School of Public Health, Boston, MA, US; [6]Botswana Harvard AIDS Institute, Gaborone, Botswana; [7]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US

877 Hospitalizations Among Uninfected Children Exposed or Unexposed to HIV – A Nationwide Cohort Study

Ellen M. Larsen[1]; Marie Helleberg[2]; Sannie Nordly[3]; Nina Weis[3]; Vibeke Rosenfeldt[3]; Merete Storgaard[4]; Gitte Pedersen[5]; Isik S. Johansen[6]; Suzanne Lunding[1]; Terese L. Katzenstein[2]

[1]Nordsjællands Hospital, Hillerød, Denmark; [2]Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [3]Copenhagen University Hospital, Hvidovre, Hvidovre, Denmark; [4]Aarhus University Hospital, Skejby, Aarhus, Denmark; [5]Aalborg University Hospital, Aalborg, Denmark; [6]Odense University Hospital, Odense, Denmark

878 Reassuring Birth Outcomes Data With Atripla Used for PMTCT in Botswana

Rebecca Zash[1]; Jennifer Y. Chen[2]; Sajini Souda[3]; Scott Dryden-Peterson[4]; Shahin Lockman[4]; Mompati Mmalane[3]; Joseph Makhema[3]; Max Essex[5]; Roger Shapiro[1]

[1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Botswana Harvard AIDS Institute, Gaborone, Botswana; [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [5]Harvard School of Public Health, Boston, MA, US

879 Growth and Bone Markers in Malawian Infants Pre- and Postnatally Exposed to Tenofovir

Giuseppe Liotta[2]; Marco Floridia[1]; **Mauro Andreotti**[1]; Haswell Jere[3]; Clementina Galluzzo[1]; Sandro Mancinelli[2]; Maria Cristina Marazzi[4]; Stefano Vella[1]; Marina Giuliano[1]; Leonardo Palombi[2]

[1]Istituto Superiore di Sanità, Rome, Italy; [2]University of Tor Vergata, Rome, Italy; [3]Community of S.Egidio, Blantyre, Malawi; [4]Lumsa University, Rome, Italy

880 Lower Insulin, Acylcarnitines, and Branch-Chain Amino Acids in HIV-Exposed Infants

Jennifer Jao[1]; Brian Kirmse[2]; Chunli Yu[3]; Fanny Epie[4]; Emmanuel Nshom[4]; Rhoda Sperling[5]; Elaine J. Abrams[6]; Derek LeRoith[7]; Mitchell Geffner[8]; Irwin Kurland[9]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, US; [2]Children's National Health System, Washington, DC, US; [3]Icahn School of Medicine at Mount Sinai, New York, NY, US; [4]Cameroon Baptist Convention Health Services, Bamenda, Cameroon; [5]Icahn School of Medicine at Mount Sinai, New York, NY, US; [6]ICAP at Columbia University, New York, NY, US; [7]Icahn School of Medicine at Mount Sinai, New York, NY, US; [8]Keck School of Medicine at University of Southern California, Los Angeles, CA, US; [9]Albert Einstein College of Medicine, New York, NY, US

881 No Effect of Maternal HIV and In-Utero cART on Infant Leukocyte Telomere Length

Abhinav Ajaykumar[1]; Hugo Soudeyns[2]; Fatima Kakkar[2]; Jason Brophy[3]; Ari Bitnun[4]; Ariane Alimenti[1]; Deborah Money[1]; Arianne Albert[5]; Hélène C. Côté[1]
On behalf of the CIHR Team in Cellular Aging and HIV Comorbidities in Women and Children (CARMA)

[1]University of British Columbia, Vancouver, Canada; [2]Université de Montréal, Montreal, Canada; [3]University of Ottawa, Ottawa, Canada; [4]University of Toronto, Toronto, Canada; [5]Women's Health Research Institute, Vancouver, Canada

882 Long-Term Effects of In Utero ARV Exposure on Cardiac Function in HIV-Exposed Uninfected Youth

Vitor C. Guerra[1]; Erin Leister[2]; Paige L. Williams[2]; Steven E. Lipshultz[3]; Russell Van Dyke[1]; Rohan Hazra[4]; Steven D. Colan[5]

[1]Tulane University, New Orleans, LA, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]Wayne State University School of Medicine, Detroit, MI, US; [4]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US; [5]Boston Children's Hospital, Harvard Medical School, Boston, MA, US

Session P-T5 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Coinfections Among HIV-Exposed Infants and Children

883 Burden of Malaria in a Birth Cohort of HIV-Exposed Ugandan Infants

Abel Kakuru[2]; Paul Natureeba[2]; Albert Plenty[1]; Edwin Charlebois[1]; Deborah Cohan[1]; Tamara Clark[1]; Diane Havlir[1]; Moses R. Kamya[3]; Grant Dorsey[1]; **Theodore Ruel**[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Makerere University-University of California, San Francisco Research Collaboration, Kampala, Uganda; [3]Makerere University College of Health Sciences, Kampala, Uganda

884 CMV Transmission From HIV-infected Women Randomized to Formula Versus Breastfeeding

Barbra Richardson[1]; Grace John-Stewart[1]; Vincent Emery[2]; Claire Atkinson[4]; Ruth Nduati[3]; Kristjana H. Ásbjörnsdóttir[1]; Julie M. Overbaugh[5]; Michael Boeckh[5]; **Jennifer A. Slyker**[1]

[1]University of Washington, Seattle, WA, US; [2]University of Surrey, Guildford, United Kingdom; [3]University of Nairobi, Nairobi, Kenya; [4]University College London, London, United Kingdom; [5]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US

885 Is the Prevalence of *M. tuberculosis* Infection Higher in HIV-Exposed Children?

Palwasha Y. Khan[1]; Katherine L. Fielding[1]; Dominic Mulawa[2]; Regina Chiumya[2]; Themba Mzembe[2]; Olivier Koole[1]; Judith R. Glynn[1]; Amelia C. Crampin[1]

[1]London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]Karonga Prevention Study, Karonga, Malawi

TUESDAY, FEBRUARY 24, 2015

Session P-T6 Poster Session — Poster Hall

2:30 pm – 4:00 pm

ART Adherence, Adverse Effects, and Retention Among Pregnant Women and Infants

886 ARV Adherence Associated with Reduced Breastmilk HIV Viral Load and HIV Transmission

Nicole L. Davis[4]; **William C. Miller**[4]; Michael G. Hudgens[4]; Charles S. Chasela[1]; Dorothy Sichali[2]; Julie A. Nelson[4]; Joseph Rigdon[4]; Sascha R. Ellington[3]; Athena P. Kourtis[3]; Charles M. van der Horst[4]
BAN study team

[1]University of Witswatersand, Johannesburg, South Africa; [2]UNC Project-Malawi, Lilongwe, Malawi; [3]US Centers for Disease Control and Prevention (CDC), Atlantaq, GA, US; [4]University of North Carolina, Chapel Hill, NC, US

887 Peripartum Hair Levels of Antiretrovirals Predict Viral Suppression in Ugandan Women

Catherine A. Koss[1]; Peter Bacchetti[1]; Deborah Cohan[1]; Paul Natureeba[1]; Howard Horng[1]; Tamara Clark[1]; Edwin Charlebois[1]; Moses R. Kamya[2]; Diane Havlir[1]; Monica Gandhi[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Makerere University College of Health Sciences, Kampala, Uganda

888 Side Effects and Treatment Adherence After ART Initiation in Pregnancy in South Africa

Tamsin Phillips[1]; Allison V. Zerbe[2]; Agnes Ronan[1]; Claude A. Mellins[3]; Robert H. Remien[3]; James A. McIntyre[4]; Greg Petro[1]; Elaine J. Abrams[2]; Landon Myer[1]

[1]University of Cape Town, Cape Town, South Africa; [2]ICAP at Columbia University, New York, NY, US; [3]New York State Psychiatric Institute and Columbia University, New York, NY, US; [4]Anova Health Institute, Johannesburg, South Africa

889 Efficacy of Mobile Phone Use on Adherence to Nevirapine Prophylaxis and Retention in Care Among HIV-Exposed Infants

Lilian M. Kebaya; Dalton Wamalwa; Nyambura Kariuki; Bashir Admani; Ruth W. Nduati

University of Nairobi, Nairobi, Kenya

890 HIV Care Continuum for Postpartum Women in Philadelphia: Barriers and Facilitators

Joella W. Adams[1]; Kathleen Brady[1]; Yvonne Michael[3]; Baligh R. Yehia[4]; Florence Momplaisir[2]

[1]Philadelphia Department of Public Health, Philadelphia, PA, US; [2]Drexel University College of Medicine, Philadelphia, PA, US; [3]Drexel University School of Public Health, Philadelphia, PA, US; [4]University of Pennsylvania, Philadelphia, PA, US

Session P-T7 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Pharmacokinetics and Safety of ART During Pregnancy

891 Raltegravir Plasma Concentrations on HIV-1 Infected Pregnant Women

Emilie Belissa; Amine Benchikh; Charlotte Charpentier; Morgane Valentin; Agnes Bourgeois-Moine; Sylvie Lariven; Florence Damond; Yazdan Yazdanpanah; Sophie Matheron; **Gilles Peytavin**

APHP, Bichat-Claude Bernard Hospital, Paris, France

892 Etravirine Pharmacokinetics During Pregnancy and Postpartum

Brookie M. Best[1]; Angela Colbers[2]; Jiajia Wang[3]; Graham Taylor[4]; Alice Stek[5]; Marjo van Kasteren[6]; Mark Mirochnick[7]; David Burger[2]
On behalf of the IMPAACT P1026s Protocol Team and the PANNA Network

[1]University of California San Diego, San Diego, CA, US; [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; [3]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, US; [4]Imperial College Healthcare NHS Trust, London, United Kingdom; [5]University of Southern California School of Medicine, Los Angeles, CA, US; [6]St. Elisabeth Hospital, Tilburg, Netherlands; [7]Boston University School of Medicine, Boston, MA, US

893 Pharmacokinetics of Etravirine in HIV-1–Infected Pregnant Women

M Ramgopal[1]; O Osiyemi[2]; C Zorrilla[3]; HM Crauwels[4]; R Ryan[5]; K Brown[6]; V Hillewaert[7]; B Baugh[6]

[1]Midway Immunology and Research Center, Fort Pierce, FL, US; [2]Triple O Research Institute PA, West Palm Beach, FL, US; [3]University of Puerto Rico School of Medicine, San Juan, US; [4]Janssen Infectious Diseases, Beerse, Belgium; [5]Janssen Research & Development, Titusville, NJ, US; [6]Janssen Therapeutics, Titusville, NJ, US; [7]Janssen Research & Development, Beerse, Belgium

894 Pharmacokinetics of Rilpivirine in HIV-Infected Women During Pregnancy and Postpartum

Mark Mirochnick[1]; Brookie M. Best[2]; Alice Stek[3]; Regis Kreitchmann[8]; Jiajia Wang[4]; David Shapiro[4]; Elizabeth Smith[5]; Lynne Mofenson[6]; Tim R. Cressey[7]; Edmund Capparelli[2]

[1]Boston University School of Medicine, Hingham, MA, US; [2]University of California San Diego, San Diego, CA, US; [3]University of Southern California, Los Angeles, CA, US; [4]Harvard School of Public Health, Boston, MA, US; [5]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US; [6]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US; [7]Harvard School of Public Health/Chiang Mai University, Chang Mai, Thailand; [8]Irmandade da Santa Casa de Misericordia de Porto Alegre, Porte Alegre, Brazil

894-A Pharmacokinetics of Rifampin in TB/HIV-Coinfected Women: Does Pregnancy Matter?

Paolo Denti[1], Helen McIlleron[1], Neil Martinson[2], Silvia Cohn[2], Jennifer Hoffmann[2], Richard Chaisson[2], Kelly Dooley[2], Fildah Mashabela[3], Regina Msandiwa[3]
On behalf of the TSHEPISO Study Team

[1]Division of Clinical Pharmacology, University of Cape Town, Cape Town, South Africa; [2]Johns Hopkins University School of Medicine, Baltimore, Maryland, United States; [3]Perinatal HIV Research Unit, University of the Witwatersrand, Soweto, South Africa

Session P-T8 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Planning and Preventing Pregnancy

895 Safer Conception Delayed by Lack of HIV Viral Suppression

Sheree R. Schwartz[1]; Rebecca Phofa[2]; Nompumelelo Yende[2]; Jean Bassett[2]; Nora West[2]; Ian Sanne[3]; Annelies Van Rie[1]

[1]University of North Carolina, Chapel Hill, NC, US; [2]Witkoppen Health and Welfare Centre, Johannesburg, South Africa; [3]University of the Witwatersrand, Johannesburg, South Africa

896 Preventing Unintended Pregnancy and HIV: The HIV Treatment Cascade and Contraceptive Choices

Julia Raifman[1]; Terusha Chetty[2]; Frank Tanser[2]; Tinofa Mutevedzi[2]; Philippa Matthews[2]; Kobus Herbst[2]; Deenan Pillay[2]; Till Barnighausen[1]

[1]Harvard School of Public Health, Washington, DC, US; [2]Africa Centre for Health and Population Studies, Mtubatuba, South Africa

THURSDAY, FEBRUARY 26, 2015

Session P-T9 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Mechanisms of MTCT and Maternal/Infant Health

897 HIV Target Cells and Altered Microbiome Associated With Mixed Feeding in South Africa

Lianna F. Wood[1]; Cosette LeCiel[2]; Heather Jaspan[3]; Donald Sodora[2]

[1]University of Washington, Seattle, WA, US; [2]Seattle BioMed, Seattle, WA, US; [3]Seattle Children's Hospital, Seattle, WA, US

898 Role of Type 1 IFNs in the Control of HIV-1 Infection at the Feto-Maternal Interface

Erica L. Johnson; Sahithi Boggavarapu; Elan S. Johnson; Asim A. Lal; Siddhartha Bhaumik; Murali-Krishna Kaja; Rana Chakraborty

Emory University School of Medicine, Atlanta, GA, US

899 Immune Activation During Pregnancy and Postpartum Period in Treated HIV+ Ugandans

Peter W. Hunt[1]; Helen Byakwaga[2]; Yap Boum[2]; Lynn T. Matthews[3]; Tricia H. Burdo[4]; Yong Huang[1]; Annet Kembabazi[2]; Angela Kaida[5]; David R. Bangsberg[3]; Jeffrey Martin[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Mbarara University of Science and Technology, Mbarara, Uganda; [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [4]Boston College, Boston, MA, US; [5]Simon Fraser University, Vancouver, Canada

900 T-Cell Activation and Exhaustion in HIV-Infected and HIV-Uninfected Pregnant Women

Christina Fiske; Vlada Melekhin; Fernanda Maruri; Cindy Hager; Louise Barnett; Timothy Sterling; Spyros Kalams

Vanderbilt University School of Medicine, Nashville, TN, US

901 HIV and Smoking Associated with Shorter Telomere Length in a Cohort of Pregnant Women

Sara Saberi[1]; Beheroze Sattha[1]; Evelyn Maan[2]; Julie Van Schalkwyk[3]; Deborah Money[1]; Hélène Côté[1]
On behalf of the CIHR Team in Cellular Aging and HIV Comorbidities in Women and Children (CARMA)

[1]University of British Columbia, Vancouver, Canada; [2]BC Women's Hospital and Health Centre, Vancouver, Canada; [3]Women's Health Research Institute, Vancouver, Canada

902 Low Prolactin and High 20αHSD May Contribute to cART-Induced P4 Deficits in Pregnancy

Eszter Papp; **Lena Serghides**
AAPH Team

Toronto General Research Institute, Toronto, Canada

TUESDAY, FEBRUARY 24, 2015

Session P-T10 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Immune Mechanisms in MTCT

903 Generating HIV Neutralization in Milk With Neutralizing IgG/dIgA Antibodies Infusion

Genevieve Fouda[1]; Josh Eudailey[1]; Erika Kunz[1]; Joshua Amos[1]; Jonathan Himes[1]; Lisa Colvin[1]; Xinyue Wang[2]; Keith Reimann[2]; Barton Haynes[1]; Sallie Permar[1]

[1]Duke University, Durham, NC, US; [2]University of Massachusetts Medical School, Boston, MA, US

904 Specificity of V3-specific Neutralizing Responses in HIV-1 Infected Women

David R. Martinez; Genevieve Fouda; Nathan Vandergrift; Celia LaBranch; David Montefiori; Xiaoying Shen; Thomas Denny; Georgia Tomaras; Sallie Permar

Duke Human Vaccine Institute, Durhamc, NC, US

905 Broad, Highly Avid Vaccine-Elicited Anti-V1V2 IgG Responses in HIV-Exposed Infants

Genevieve Fouda[1]; Coleen Cunningham[1]; Elizabeth McFarland[2]; Bill Borkowsky[3]; Nicole Yates[1]; Erin McGuire[1]; Hua-Xin Liao[1]; Barton Haynes[1]; Georgia Tomaras[1]; Sallie Permar[1]

[1]Duke University, Durham, NC, US; [2]University of Colorado, Aurora, CO, US; [3]New York University, New York, NY, US

906 Maternal Neutralization Escape Virus Variants Do Not Predict Infant HIV Infection Risk

Caitlin Milligan[1]; Maxwel Omenda[1]; Vrasha Chohan[1]; Katherine Odem-Davis[1]; Barbra A. Richardson[1]; Ruth W. Nduati[2]; Julie M. Overbaugh[1]

[1]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [2]University of Nairobi, Nairobi, Kenya

Session P-T11 Poster Session — Poster Hall

2:30 pm – 4:00 pm

PMTCT-Associated Drug Resistance in Women and Infants

907 ART Failure and Resistance Among Pregnant and Post-Partum Women in South Africa

Christopher J. Hoffmann[1]; Silvia Cohn[1]; Fildah Mashabela[2]; Jennifer Hoffmann[1]; **Kelly E. Dooley**[1]; Richard E. Chaisson[1]; Neil Martinson[2]
the TSHEPISO Study Team

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Perinatal HIV Research Unit (PHRU), Johannesburg, South Africa

908 High Prevalence of HIV-1 Drug-Resistance Mutations in Subtype C Transmitting Mothers Detected Using 454 Ultra-Deep Sequencing

Johanna Ledwaba[1]; Anna Salimo[1]; Karl Technau[4]; Simon Travers[3]; Lynn Morris[1]; Gillian Hunt[1]; Louise Kuhn[2]

[1]National Institute for Communicable Diseases, National Health Laboratory Service, Sandringham, South Africa; [2]Columbia University, New York, NY, US; [3]University of the Western Cape, Modderdam, South Africa; [4]University of the Witwatersrand, Johannesburg, South Africa

909 NVP Resistance in Infants Infected by HIV-1 via Breastfeeding in the BAN Study

Julie A. Nelson[1]; Ali Fokar[1]; Michael G. Hudgens[1]; Kara J. Compliment[1]; Gerald Tegha[2]; Deborah Kamwendo[2]; Athena P. Kourtis[3]; Denise J. Jamieson[3]; Charles M. van der Horst[1]; Susan A. Fiscus[1]

[1]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, US; [2]University of North Carolina Project–Malawi, Lilongwe, Malawi; [3]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Session P-U1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HIV Diagnosis in Infants and Children

910 Birth HIV PCR Testing in South Africa: Diagnostic Challenges and Risk Factor Analysis

Karl-Günter Technau[1]; Louise Kuhn[2]; Lucia Hans[3]; Sergio Carmona[3]; Ashraf Coovadia[1]; Gayle Sherman[4]

[1]University of the Witwatersrand, Johannesburg, South Africa; [2]Columbia University, New York, NY, US; [3]National Health Laboratory Service, Johannesburg, South Africa; [4]National Institute for Communicable Diseases, Johannesburg, South Africa

911 System Gaps Result in Late Diagnosis and Treatment of Children With HIV in Hospital

Irene N. Njuguna[3]; Anjuli D. Wagner[1]; Vincent Otieno[3]; Lisa Cranmer[2]; Judy Adhiambo[3]; Sarah Benki-Nugent[1]; Elizabeth Maleche-Obimbo[3]; Jennifer A. Slyker[1]; Dalton Wamalwa[3]; Grace John-Stewart[1]

[1]University of Washington, Seattle, Kenya; [2]Emory University School of Medicine, Atlanta, GA, US; [3]University of Nairobi, Nairobi, Kenya

Session P-U2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Early ART and HIV Persistence

912 Early Infant Antiretroviral Therapy Reduces Transcriptionally Active HIV Persistence

Gert U. van Zyl[1]; Margaret A. Bedison[2]; Anita Janse van Rensburg[3]; Barbara Laughton[3]; Mark F. Cotton[3]; John W. Mellors[2]

[1]Stellenbosch University and National Health Laboratory Service, Parow, South Africa; [2]University of Pittsburgh, Pittsburgh, PA, US; [3]Stellenbosch University and Tygerberg Academic Hospital, Cape Town, South Africa

WEDNESDAY, FEBRUARY 25, 2015

Session P-U3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Treatment Outcomes Among Children and Youth With HIV

913 Immunodeficiency at the Start of ART in Children: A Global View

Klea Panayidou[1]; Ali Judd[3]

On behalf of the IeDEA Collaboration and the COHERE Collaboration

[1]University of Bern, Bern, Switzerland; [2]University of Copenhagen, Copenhagen, Denmark; [3]University College London, London, United Kingdom

914 Immune Recovery at 5 Years on ART in HIV+ Children From Four African Countries

Chloe A. Teasdale; Ruby Fayorsey; Zenebe Melaku; Duncan Chege; Catarina Casalini; Thresia Sebastian; **Elaine J. Abrams**

ICAP at Columbia University, New York, NY, US

915 Antiretroviral Therapy in Severely Malnourished, HIV-Infected Children in Asia

David C. Boettiger[1]; Linda Aurpibul[2]; Dina Muktiarti[3]; Siew Fong[4]; Pagakrong Lumbiganon[5]; Saphonn Vonthanak[6]; Nguyen Van Lam[7]; Rawiwan Hansudewechakul[8]; Azar Kariminia[1]

On behalf of TREAT Asia Pediatric HIV Observational Database

[1]University of New South Wales, Sydney, Australia; [2]Chiang Mai University, Chiang Mai, Thailand; [3]Cipto Mangunkusumo General Hospital, Jakarta, Indonesia; [4]Hospital Likas, Kota Kinabalu, Malaysia; [5]Khon Kaen University, Khon Kaen, Thailand; [6]National Centre for HIV/AIDS Dermatology and STDs, Phnom Penh, Cambodia; [7]National Hospital of Pediatrics, Hanoi, Viet Nam; [8]Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand

916 Pubertal Development in HIV-Infected African Children on First-Line Antiretroviral Therapy

Mutsa F. Bwakura Dangarembizi

On behalf of the ARROW Trial Team

University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe

917 Mortality of HIV-Infected Youth in the Combination Antiretroviral Therapy (cART) Era

Gayatri Mirani[1]; Paige L. Williams[2]; Miriam Chernoff[2]; Mark Abzug[6]; Myron Levin[3]; James Oleske[4]; George Seage[2]; Rohan Hazra[5]; Russell B. Van Dyke[1]

On behalf of the International Maternal Pediatric Adolsescent AIDS Clinical Trials (IMPAACT) Network P1074 Study Team

[1]Tulane University Health Sciences Center, New Orleans, LA, US; [2]Center for Biostatistics in AIDS Research Harvard School of Public Health, Boston, MA, US; [3]University of Colorado Anschutz Medical Campus, Aurora, CO, US; [4]Division of Pediatrics Allergy, Immunology & Infectious Diseases, Newark, NJ, US; [5]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US; [6]University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO, US; [7]IMPAACT Operations Center FHI 360, Durham, NC, US

918 Transition to Adult Units: Situation and Evolution of Vertically HIV Infected Youths in Spain

Talía Sainz[1]; Carolina Fernández McPhee[2]; Santiago Jimenez de Ory[1]; Maria Isabel Gonzalez-Tome[3]; Rafael Rubio[3]; Jose I Bernardino[4]; Santiago Moreno[2]; Jose Antonio Iribarren[5]; Belen Alejos[6]; Marisa Navarro[7]

On behalf of the Spanish Cohort of AIDS Research (CORIS) and the Pediatric Spanish Cohort of HIV-infected Children (CoRISpe)

[1]Hospital Universitario Gregorio Marañón, Madrid, Spain; [2]Hospital Universitario Ramon y Cajal, Madrid, Spain; [3]12 de Octubre Hospital, Madrid, Spain; [4]La Paz University Hospital, Madrid, Spain; [5]Hospital de Donostia, San Sebastian, Spain; [6]Centro Nacional de Epidemiología, ISCIII, Madrid, Spain; [7]Hospital Gregorio Marañon, Madrid, Spain

Session P-U4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Treatment and Monitoring Strategies in Children

919 Long-Term Consequences of Planned Treatment Interruption in HIV-1–Infected Children

Riccardo Freguja[1]; Hahhah Poulson[2]; Paola Del Bianco[3]; Alexandra Compagnucci[4]; Yacine Saidi[4]; Carlo Giaquinto[5]; Lynda Harper[6]; Diana M. Gibb[6]; Nigel J. Klein[2]; Anita De Rossi[1]

[1]1 AIDS Reference Center, Section of Oncology and Immunology, Padova, Italy; [2]Institute of Child Health, London, United Kingdom; [3]Istituto Oncologico Veneto-IRCCS, Padova, Italy; [4]Inserm SC10, Paris, France; [5]Department of Mother and Child Health, Padova, Italy; [6]Medical Research Council, London, United Kingdom

920 Can CD4 Monitoring in Virologically Suppressed Children be Reduced or Stopped?

Mary-Ann Davies[1]; Helena Rabie[2]; Geoff Fatti[3]; Kathryn Stinson[1]; **Karl-Günter Technau**[4]; Shobna Sawry[5]; Brian Eley[6]; Lynne Mofenson[7]; Andrew Boulle[1]; IeDEA Southern Africa[8]

[1]University of Cape Town, Cape Town, South Africa; [2]University of Stellenbosch, Cape Town, South Africa; [3]Kheth'Impilo, Cape Town, South Africa; [4]University of the Witwatersrand, Johannesburg, South Africa; [5]University of Witwatersrand, Johannesburg, South Africa; [6]University of Cape Town, Cape Town, South Africa; [7]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US; [8]Univeristy of Cape Town and University of Bern, Cape Town, South Africa

TUESDAY, FEBRUARY 24, 2015

Session P-U5 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Determinants of Disease Progression in Children

921 Impact of Sex Differences on Disease Outcome in Pediatric HIV in South Africa

Masahiko Mori[1]; Emily Adland[1]; Alice Swordy[1]; Maximilian Muenchhoff[1]; Nora Lavandier[1]; Jacob Hurst[1]; Thumbi Ndung'u[2]; Andy Prendergast[3]; Philip J. Goulder[1]; Pieter Jooste[4]

[1]University of Oxford, Oxford, United Kingdom; [2]University of KwaZulu-Natal, Durban, South Africa; [3]Queen Mary University of London, London, United Kingdom; [4]Kimberley Hospital, Durban, South Africa

922 CD31 Expression on CD4 Cells Predicts Clinical Course of HIV in a Perinatally HIV-Infected Cohort

Ramia Zakhour[1]; Gilhen Rodriguez[2]; Cynthia Bell[2]; Guenet Degaffe[2]; Laura Benjamins[2]; Gabriela DelBianco[2]; Elizabeth Donnachie[2]; Tran Dat[2]; Gloria P. Heresi[2]; James R. Murphy[2]

[1]University of Texas, Houston, TX, US; [2]UTHealth Medical School, Houston, TX, US

923 Premature Aging and Immune Senescence in HIV-1-Infected Children

Ketty Gianesin[1]; Antoni Noguera-Julian[2]; Marisa Zanchetta[3]; Osvalda Rampon[1]; Clàudia Fortuny[2]; Mireia Camós[2]; Carlo Giaquinto[1]; Anita De Rossi[1]

[1]University of Padova, Padova, Italy; [2]Hospital Sant Joan de Déu-Universitat de Barcelona, Barcelona, Spain; [3]Istituto Oncologico Veneto–IRCCS, Padova, Italy

924 *KIR/HLA* Alleles Alter CD4$^+$ Lymphocyte Count and Viral Load in HIV-Infected Children

Kumud Singh[1]; Min Qin[2]; Sean Brummel[2]; Konstantia Angelidou[2]; Rodney Trout[1]; Terrence Fenton[2]; Stephen Spector[1]

[1]University of California San Diego, La Jolla, CA, US; [2]Harvard School of Public Health, Boston, MA, US

THURSDAY, FEBRUARY 26, 2015

Session P-U6 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Complications of HIV and ART: Pulmonary and Cardiovascular Outcomes

925 Arterial Stiffness in HIV+ Youth and Associations With HIV-Related Variables

Allison R. Eckard[1]; Julia C. Rosebush[1]; Mary Ann O'Riordan[2]; Christopher T. Longenecker[2]; Bridget Wynn[1]; Monika Uribe Leitz[1]; Danielle Labbato[2]; Norma Storer[2]; Bruce Kinley[2]; Grace A. McComsey[2]

[1]Emory University School of Medicine, Atlanta, GA, US; [2]Case Western Reserve University, Cleveland, OH, US

926 Does Early ART Normalize Pulse-Wave Velocity in Children? Evidence From CHER Cohort

Steve Innes[1]; Zukiswa Magogotya[1]; Philip Herbst[1]; Mark F. Cotton[1]; Barbara Laughton[1]; Sara Browne[2]; Richard Haubrich[2]

[1]Stellenbosch University, Cape Town, South Africa; [2]University of California San Diego, San Deigo, CA, US

927 The Impact of HIV and ART on Markers of Inflammation, Vascular Injury and Disordered Thrombogenesis in Children

Julia M. Kenny[1]; Sarah Walker[1]; Adrian Cook[1]; Victor Musiime[2]; Priscilla Wavamunno[2]; Florence Odongo[2]; Grace Mirembe[2]; Dorica Masaku[3]; Diana M. Gibb[1]; Nigel J. Klein[1]

[1]University College London, London, United Kingdom; [2]Joint Clinical Resarch Centre, Kampala, Uganda; [3]University Teaching Hospital, Lusaka, Zambia

928 T-Cell Activation and E-Selectin Associated With Coronary Plaque in HIV-Infected Youth

Julia B. Purdy; Aylin Unsal; Khaled Abd-Elmoniem; Adam Rupert; Joseph A. Kovacs; Rohan Hazra; Ahmed Gharib; Colleen Hadigan

National Institutes of Health, Bethesda, MD, US

929 High Prevalence of Dyslipidemia and Insulin Resistance in African Children on ART

Steve Innes[1]; Kameelah L. Abdullah[2]; Richard Haubrich[2]; Sara Browne[2]; Mark F. Cotton[1]

[1]Stellenbosch University, Cape Town, South Africa; [2]University of California San Diego, San Deigo, CA, US

930 Growth and Lipid Profiles in a South African Cohort of HIV$^+$ Children and HIV$^-$ Controls

Sarah Ramteke[1]; Stephanie Shiau[1]; Marc Foca[1]; Renate Strehlau[2]; Francoise Pinillos[2]; Faeezah Patel[2]; Avy Violari[3]; Afaaf Liberty[3]; Stephen M. Arpadi[1]; Louise Kuhn[1]

[1]Columbia University, New York, NY, US; [2]University of the Witwatersrand, Johannesburg, South Africa; [3]University of Witwatersrand, Johannesburg, South Africa

Session P-U7 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Complications of HIV and ART: Bones, Brains, and Kidneys

931 Vitamin D Status and Bone Outcomes in Perinatally HIV-Infected Children

Denise L. Jacobson[1]; Mitchell Geffner[2]; Charles B. Stephensen[3]; Rohan Hazra[4]; Kunjal Patel[8]; Tracie L. Miller[5]; Russell B. Van Dyke[6]; Angela Ellis[9]; Linda A. DiMeglio[7]
For the Pediatric HIV/AIDS Cohort Study

[1]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [2]Children's Hospital Los Angeles, Keck School of Medicine, Los Angeles, CA, US; [3]USDA, Davis, CA, US; [4]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, US; [5]University of Miami, Miami, FL, US; [6]Tulane University School of Medicine, New Orleans, LA, US; [7]Indiana University, School of Medicine, Indianapolis, IN, US; [8]Harvard School of Public Health, Boston, MA, US; [9]Frontier Science and Research Foundation, Amherst, NY, US

932 Bone Quality by Ultrasonometry in South African HIV+ Children and HIV- Controls

Stephen M. Arpadi[1]; Stephanie Shiau[1]; Renate Strehlau[2]; Francoise Pinillos[2]; Faeezah Patel[2]; Louise Kuhn[1]; Ashraf Coovadia[2]; Sarah Ramteke[1]; Jonathan Kaufman[3]; Michael T. Yin[1]

[1]Columbia University, New York, NY, US; [2]University of the Witwatersrand, Johannesburg, South Africa; [3]Mount Sinai School of Medicine, New York, NY, US

933 APOL1 Gene Variants and Chronic Kidney Disease in Perinatally HIV-Infected Youth

Murli Purswani[1]; Kunjal Patel[2]; Cheryl Winkler[3]; Stephen Spector[4]; Rohan Hazra[5]; George Seage[2]; Lynne Mofenson[5]; Gwendolyn Scott[6]; Russell Van Dyke[7]; Jeffrey Kopp[8]
For the Pediatric HIV/AIDS Cohort Study (PHACS)

[1]Albert Einstein College of Medicine, Bronx, NY, US; [2]Harvard School of Public Health, Boston, MA, US; [3]National Cancer Institute (NCI), Bethesda, MD, US; [4]University of California San Diego, San Diego, CA, US; [5]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US; [6]University of Miami, Miami, FL, US; [7]Tulane University, New Orleans, LA, US; [8]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, US

934 Cystatin C Is a Marker for Both Inflammation and Renal Function in HIV+ Children

Àngela Deyà-Martínez[1]; **Clàudia Fortuny**[1]; Pere Soler-Palacín[2]; Olaf Neth[3]; Emilia Sánchez[4]; Andrea Martín-Nalda[2]; Lola Falcón-Neyra[3]; Anna Vila[1]; Anna Valls[1]; Antoni Noguera-Julian[1]

[1]Hospital Sant Joan de Déu, Esplugues, Spain; [2]Hospital Vall d'Hebrón, Barcelona, Spain; [3]Hospital Virgén del Rocío, Sevilla, Spain; [4]Universitat Ramon Llull, BArcelona, Spain

935 Cognitive Performance and Intracerebral Findings in Perinatally HIV-Infected Children

Sophie Cohen[1]; Matthan W. Caan[2]; Jacqueline A. ter Stege[3]; Henriette J. Scherpbier[1]; Taco W. Kuijpers[1]; Peter Reiss[2]; Gert J. Geurtsen[2]; Charles B. Majoie[2]; Ben Schmand[2]; Dasja Pajkrt[1]

[1]Emma Children's Hospital AMC, Amsterdam, Netherlands; [2]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [3]Emma Children's Hospital, Amsterdam, Netherlands

936 Executive Functions Among Perinatally HIV-Exposed and HIV-Infected Youth

Sharon L. Nichols[1]; Miriam Chernoff[2]; Kathleen M. Malee[3]; Patricia A. Sirois[4]; Paige L. Williams[2]; Betsy L. Kammerer[5]
the Memory Substudy Team of the Pediatric HIV/AIDS Cohort Study (PHACS)

[1]University of California, San Diego, La Jolla, CA, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]Northwestern University Feinberg School of Medicine, Chicago, IL, US; [4]Tulane University School of Medicine, New Orleans, LA, US; [5]Children's Hospital Boston, Boston, MA, US

937 Sleep Disturbances in a Cohort of HIV-Infected Children and Adolescents on Antiretroviral Treatment: NeuroCoRISpeS

Cristina García-Navarro[1]; Santiago Jiménez de Ory[2]; Maria Luisa Navarro Gomez[2]; José Tomás Ramos Amador[6]; Maria Jose Mellado[3]; Luis Prieto[5]; Pablo Rojo Conejo[1]; Esmeralda Nuñez[4]; **María Isabel González-Tomé**[1]
On behalf of the CoRISpeS,ÄìMadrid Cohort

[1]Hospital Universitario 12 de Octubre, Madrid, Spain; [2]Hospital Universitario Gregorio Marañón, Madrid, Spain; [3]Hospital Universitario La Paz, Madrid, Spain; [4]Hospital Regional Universitario Carlos Haya, Malaga, Spain; [5]Hospital Universitario de Getafe, Getafe, Spain; [6]Hospital Universitario Clinico San Carlos, Madrid, Spain; [7]Madrid, Madrid, Spain

WEDNESDAY, FEBRUARY 25, 2015

Session P-U8 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Tuberculosis and Other Coinfections in Children With HIV

938 Tuberculosis Among Children on Antiretroviral Therapy in Swaziland, 2004-2012

Melissa A. Briggs[1]; Andrew Auld[1]; Harrison Kamiru[2]; Harriet Nuwagaba-Biribonwoha[2]; Velephi Okello[3]; George Bicego[1]; Andrew L. Baughman[1]; Simon Agolory[1]; Tedd V. Ellerbrock[1]; Peter Ehrenkranz[4]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]Mailman School of Public Health, New York, NY, US; [3]Swaziland Ministry of Health, Mbabane, Swaziland; [4]US Centers for Disease Control and Prevention (CDC), Mbabane, Swaziland

939 Mycobacterium TB Disease in HIV-Infected Children Receiving LPV/r or NVP-Based ART

Moherndran Archary[1]; Linda Barlow-Mosha[2]; Avy Violari[3]; Jane Lindsey[4]; Lynne Mofenson[4]; Patrick Jean-Philipe[4]; Bonnie Zimmer[4]; Paul E Palumbo[5]

[1]University of KwaZulu-Natal, Durban, South Africa; [2]MUJHU Care Ltd/MUJHU Research Collaboration, Kampala, Uganda; [3]Perinatal HIV Research Unit, Johannesburg, South Africa; [4]Frontier Science, Amherst, NY, US; [5]Geisel School of Medicine at Dartmouth, Lebanon, NH, US

940 Safety of Rifabutin in HIV/TB-Coinfected Children on Protease Inhibitor-Based ART

Holly E. Rawizza[1]; Kristin M. Darin[2]; Kimberly K. Scarsi[3]; Biobele Brown[4]; Regina Oladokun[4]; Nkiru David[5]; Sulaimon Akanmu[6]; Oluremi Olaitan[7]; Prosper Okonkwo[7]; Phyllis Kanki[8]
On behalf of the APIN PEPFAR Team

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [2]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [3]University of Nebraska Medical Center, Omaha, NE, US; [4]University College Hospital, Ibadan, Nigeria; [5]National Institute of Medical Research, Lagos, Nigeria; [6]Lagos University Teaching Hospital, Lagos, Nigeria; [7]AIDS Prevention Initiative in Nigeria, Abuja, Nigeria; [8]Harvard School of Public Health, Boston, MA, US

941 Skin Complaints in African Children Randomized to Stop or Continue Cotrimoxazole

Andrew Prendergast[1]; Mutsa F. Bwakura Dangarembizi[2]; Peter Mugyenyi[3]; Joseph Lutaakome[4]; Adeodata Kekitiinwa[5]; Diana M. Gibb[6]; Sarah Walker[6]
On behalf of the ARROW Trial Team

[1]Queen Mary University of London, London, United Kingdom; [2]University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe; [3]JCRC, Kampala, Uganda; [4]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda; [5]Baylor-Uganda, Kampala, Uganda; [6]MRC Clinical Trials Unit at University College London, London, United Kingdom

942 Disease Progression and Response to Treatment in Vertically HIV/HVC Co-infected Patients

Talía Sainz[1]; Carolina Fernández McPhee[2]; Santiago Jimenez de Ory[1]; Pablo Rojo[3]; Maria del Carmen Otero[4]; Milagros Garcia Lopez-Hortelano[5]; Olaf Neth[7]; Jose Beceiro[8]; Maribel González Tomé[3]; María Luisa Navarro[6]
On behalf of the Spanish Cohort of HIV-Infected Children and Adolescents (CoRISpe)

[1]Hospital Universitario Gregorio Marañón, Madrid, Spain; [2]Hospital Ramón y Cajal, SEIM-Gesida, Madrid, Spain; [3]Hospital 12 de Octubre, Madrid, Spain; [4]Hospital La Fe, Valencia, Spain; [5]Hospital La Paz, Madrid, Spain; [6]Hospital Gregorio Marañón, Madrid, Spain; [7]Hospital Virgen del Rocio, Sevilla, Spain; [8]Hospital de Alcalá, Alcalá de Henares, Spain

943 Human Papillomavirus and Cervical Cytology in Perinatally Infected Asian Adolescents

Annette H. Sohn[1]; Stephen J. Kerr[2]; Rawiwan Hansudewechakul[3]; Wasana Prasitsuebsai[2]; Kulkanya Chokephaibulkit[4]; Truong V. Nguyen[5]; Thoa P. Le[6]; Thida Singtoroj[1]; Nittaya Phanuphak[7]; HPV in Adolescents Study[1]

[1]TREAT Asia/amfAR – The Foundation for AIDS Research, Bangkok, Thailand; [2]HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [3]Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand; [4]Siriraj Hospital, Mahidol University, Bangkok, Thailand; [5]Hung Vuong Hospital, Ho Chi Minh City, Viet Nam; [6]Children's Hospital 1, Ho Chi Minh City, Viet Nam; [7]SEARCH, Thai Red Cross AIDS Research Centre, Bangkok, Thailand

944 Sexually Transmitted Infections in Youth With Controlled and Uncontrolled HIV

Andres F. Camacho-Gonzalez[1]; Miriam C. Chernoff[2]; Paige L. Williams[2]; Ann Chahroudi[1]; James M. Oleske[3]; Rana Chakraborty[1]; Shirley Traite[2]; Murli U. Purswani[4]; Mark J. Abzug[5]
On behalf of the IMPAACT P1074 Study Team

[1]Emory University School of Medicine, Atlanta, GA, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]Rutgers New Jersey Medical School, Newark, NJ, US; [4]Albert Einstein College of Medicine, Division of Pediatric Infectious Diseases, Bronx Lebanon Hospital Center, Bronx, NY, US; [5]University of Colorado School of Medicine, Division of Pediatric Infectious Diseases, Aurora, CO, US; [6]International Maternal Pediatric Adolescent AIDS Clinical Trials, Durham, NC, US

TUESDAY, FEBRUARY 24, 2015

Session P-U9 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Responses to Vaccines in Children

945 Sustained Responses to Measles Revaccination in HIV-Infected Children on ART in Kenya

Laura Newman[1]; Anne Njoroge[1]; Bhavna Chohan[1]; Amalia Magaret[1]; Jonathan Gorstein[1]; Julie M. Overbaugh[2]; Dalton Wamalwa[3]; Elizabeth M. Obimbo[3]; Ruth W. Nduati[3]; Carey Farquhar[1]

[1]University of Washington, Seattle, WA, US; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [3]University of Nairobi, Nairobi, Kenya

946 T-Cell Anergy and Activation Are Associated With Suboptimal Humoral Responses to Measles Revaccination in HIV-Infected Children on Antiretroviral Therapy in Nairobi, Kenya

Matthew B. Buechler[1]; Laura Newman[2]; Bhavna Chohan[3]; Anne Njorge[5]; Dalton Wamalwa[6]; Carey Farquhar[3]

[1]University of Washington, Seattle, WA, US; [2]University of Washington, Seattle, WA, US; [3]University of Washington, Seattle, WA, US; [4]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [5]Kenyatta National Hospital, Nairobi, Kenya; [6]University of Nairobi, Nairobi, Kenya

947 Molecular Profiles of CXCR5+ CD4 Memory T Cells Associated With Flu Vaccine Response

Lesley R. de Armas[1]; Nicola Cotugno[1]; Suresh Pallikkuth[1]; Alberto Cagigi[3]; Paolo Palma[2]; Paolo Rossi[2]; Savita Pahwa[1]

[1]University of Miami Miller School of Medicine, Miami, FL, US; [2]Children's Hospital Bambino Gesu, Rome, Italy; [3]Children Hospital Bambino Gesu, Rome, Italy

948 The Potential of BCG and HIV-TB Vaccines to Exacerbate HIV-1 Pathogenesis in Infants

Kara Jensen[1]; Koen K. Van Rompay[2]; William R. Jacobs[3]; Glenn Fennelly[3]; Katie Mollan[1]; Michael G. Hudgens[1]; Mike Piatak[4]; Michelle H. Larsen[3]; Kristina De Paris[1]

[1]University of North Carolina, Chapel Hill, NC, US; [2]California National Primate Research Center, University of California, Davis, CA, US; [3]Albert Einstein College of Medicine, New York, NY, US; [4]Frederick National Laboratory, Frederick, MD, US

Session P-U10 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Pharmacokinetics, Safety, and Efficacy of ART in Children and Youth

949 Prediction of ARV Drug Clearance in Children

Frantz Foissac; Naïm Bouazza; Elodie Valade; Mailys De Sousa; Floris Fauchet; Sihem Benaboud; Deborah Hirt; Stéphane Blanche; Saïk Urien; Jean-Marc Treluyer

EA 08 Université Paris Descartes, Sorbonne Paris Cité, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, Paris, France, Paris, France

950 Use of Maraviroc in HIV-1-Infected Paediatric Patients in Clinical Practice

Claudia Palladino[1]; Maria Luisa Navarro Gomez[6]; Pere Soler-Palacín[5]; Maria Isabel Gonzalez-Tome[7]; Santiago Jimenez de Ory[6]; Maria Espiau[5]; Juan Antonio León-Leal[4]; Clàudia Fortuny[3]; Verónica Briz[2]
CoRISpe working group

[1]University of Lisbon, Lisbon, Portugal; [2]National Center for Microbiology, Madrid, Spain; [3]Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain; [4]Hospital Infantil Universitario Virgen del Rocío, Seville, Spain; [5]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [6]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [7]Hospital Universitario Doce de Octubre, Madrid, Spain

951 Safety and Pharmacokinetics of Elvitegravir in HIV-1 Infected Pediatric Subjects

Joseph M. Custodio[1]; Victor Musiime[2]; Aditya Gaur[3]; Elizabeth McFarland[4]; Wasana Prasitsuebsai[5]; Lize Hellstrom[6]; Xuelian Wei[1]; Rebecca Begley[1]; Srinivasan Ramanathan[1]; Sean R. Bennett[1]

[1]Gilead Sciences, Inc., Foster City, CA, US; [2]Joint Clinical Research Centre, Kampala, Uganda; [3]St. Jude Children's Research Hospital, Memphis, TN, US; [4]University of Colorado Denver, Aurora, CO, US; [5]HIV - NAT, Bangkok, Thailand; [6]Be Part Yoluntu Centre, Cape Town, South Africa

952 Lack of Emergent Resistance in HIV-1-Infected Adolescents on Elvitegravir-Based STRs

Danielle P. Porter; Sean R. Bennett; Erin Quirk; Michael D. Miller; Kirsten L. White

Gilead Sciences, Inc., Foster City, CA, US

953 Week-24 Data From a Phase 3 Clinical Trial of E/C/F/TAF in HIV-Infected Adolescents

Hilda Kizito[2]; Aditya Gaur[3]; Wasana Prasitsuebsai[4]; Natella Rakhmanina[5]; Eileen Lawson[1]; Yongwu Shao[1]; **Sean R. Bennett**[1]; Andrew Cheng[1]; Erin Quirk[1]

[1]Gilead Sciences, Inc., Foster City, CA, US; [2]Joint Clinical Research Centre, Kampala, Uganda; [3]St Jude Children's Research Hospital, Memphis, TN, US; [4]HIV Netherlands Australia Thailand Research Collaboration, Bangkok, Thailand; [5]Children's National Health System, Washington, DC, US

954 Efficacy and Safety of Long-Term Tenofovir DF (TDF) Therapy in HIV-Infected Children

Xavier Saez-Llorens[2]; Jaime G. Deville[3]; Ayesha Mirza[4]; Janet S. Chen[5]; Aditya Gaur[6]; Mobeen Rathore[4]; Dana Hardin[7]; Ya-Pei Liu[1]; **Erin Quirk**[1]
GS-US-104-0352 Study Team

[1]Gilead Sciences, Inc., Foster City, CA, US; [2]Hospital del Niño, Panama City, Panama; [3]University of California Los Angeles, Los Angeles, CA, US; [4]University of Florida, Jacksonville, FL, US; [5]Drexel University College of Medicine, Philadelphia, PA, US; [6]St Jude Children's Research Hospital, Memphis, TN, US; [7]Eli Lilly, Indianapolis, IN, US

955 Acceptability of Lopinavir/r Minitabs, Tablets and Syrups in HIV-Infected Children

Adeodata Kekitiinwa
CHAPAS-2

Baylor College of Medicine Children's Foundation Uganda, Kampala, Uganda

956 Therapeutic Drug Monitoring of Lopinavir in HIV-Infected Children on Second-Line ART

Linda Aurpibul[1]; Wasana Prasitsuebsai[2]; Tavitiya Sudjaritruk[3]; Pope Kosalaraksa[4]; Nia Kurniati[6]; Khanh Huu Truong[5]; Viet Chau Do[7]; Sirinya Teeraananchai[2]; Stephen J. Kerr[2]
the TASER-Pediatrics Study Group

[1]Research Institute for Health Sciences, Chaing Mai University, Chiang Mai, Thailand; [2]The HIV Netherlands Australia Thailand Research Collaboration, The Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [3]Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [4]Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand; [5]Children's Hospital 1, Ho Chi Minh City, Viet Nam; [6]Cipto Mangunkusumo General Hospital, Jakarta, Indonesia; [7]Children's Hospital 2, Ho Chi Minh City, Viet Nam

WEDNESDAY, FEBRUARY 25, 2015

Session P-V1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Postexposure Prophylaxis (PEP)

957 Significant Intolerability of Efavirenz in HIV Occupational Postexposure Prophylaxis

Surasak Wiboonchutikul[1]; Varaporn Thientong[1]; Patama Sutha[1]; Boonchai Kowadisaiburana[2]; Weerawat Manosuthi[1]

[1]Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand; [2]Bangkok Hospital, Bangkok, Thailand

958 Rilpivirine-Emtricitabine-Tenofovir for HIV Nonoccupational Postexposure Prophylaxis

Rosalind Foster[1]; John McAllister[2]; Tim R. Read[3]; Anna Pierce[4]; Robyn Richardson[2]; Anna McNulty[1]; Andrew Carr[2]
On behalf of the EPEP Study Researchers

[1]Sydney Sexual Health Centre, Sydney, Australia; [2]St Vincent's Centre for Applied Medical Research, Sydney, Australia; [3]Melbourne Sexual Health Centre, Melbourne, Australia; [4]The Alfred Hospital, Melbourne, Australia

959 Tenofovir/Emtricitabine Plus LPV/r vs MVC or Raltegravir for PEP: 2 Randomized Trials

Lorna Leal; Agathe Leon; Berta Torres; Alexy Inciarte; Constanza Lucero; Josep Mallolas; Maria Martinez-Rebollar; Ana González-Cordón; Jose M. Gatell; Felipe Garcia

Hospital Clínic Barcelona, Barcelona, Spain

960 Effects of Three Regimens of PEP on the Immune System of HIV-Seronegative Individuals

Alberto C. Guardo[1]; Lorna Leal[2]; Agathe Leon[2]; Cristina Rodriguez de Miguel[2]; Manel E. Bargallo[1]; Cristina Rovira[1]; Josep Llach[2]; Jose M. Gatell[2]; Felipe Garcia[2]; Montserrat Plana[1]

[1]L'Institut D'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; [2]Hospital Clinic, Barcelona, Spain

961 Management of Acute HIV After Initiation of Postexposure Prophylaxis: Challenges and Lessons Learned

Goli Haidari[1]; Naomi Fitzgerald[4]; Sonia Raffe[2]; Nneka Nwokolo[3]; Olamide Dosekun[1]; Mark D. Lawton[5]; Nickie Mackie[1]; Julie Fox[4]; Martin Fisher[2]; Sarah Fidler[1]

[1]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom; [2]Brighton and Sussex Hospitals NHS Trust, Brighton, United Kingdom; [3]Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom; [4]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [5]The Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, United Kingdom; [6]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom; [7]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [8]Brighton and Sussex Hospitals NHS Trust, Brighton, United Kingdom; [9]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom

THURSDAY, FEBRUARY 26, 2015

Session P-V2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

PrEP and Microbicide Challenge

962 FTC/TDF Prevents SHIV Infection in *C trachomatis* and *T vaginalis*-Infected Macaques

Jessica Radzio; Tara Henning; James Mitchell; Angela Holder; Debra Hanson; Janet McNicholl; Walid Heneine; John Papp; Ellen Kersh; Gerardo Garcia-Lerma

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

963 Impact of Sexually Transmitted Infections on the Efficacy of Tenofovir Vaginal Gel in Macaques

Natalia Makarova; Tara Henning; Andrew Taylor; Chuong Dinh; Carol Farshy; Janet McNicholl; John Papp; Walid Heneine; Ellen Kersh; **Charles W. Dobard**

US Centers for Disease Control and Prevention, Atlanta, GA, US

964 Oral Single-Dose Maraviroc Does Not Prevent Ex Vivo HIV Infection of Rectal Mucosa in Healthy HIV-1–Negative Human Volunteers in Tissue Explants.

Josep Coll[2]; José Moltó[2]; Jaume Boix[3]; Laura Else[4]; Elisabet Garcia[1]; Roger Paredes[2]; David Back[4]; Bonaventura Clotet[5]; **Cecilia Cabrera**[1]

[1]Institut de Recerca de la Sida IrsiCaixa, Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol, Barcelona, Spain; [2]Fundació Lluita Contra la SIDA, Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol, Barcelona, Spain; [3]Unidad de Endoscopia Digestiva. Hospital Universitario Germans Trias i Pujol, Barcelona, Spain; [4]Pharmacology Research Laboratories, Liverpool, United Kingdom; [5]Fundació Lluita Contra la SIDA-IRSICAIXA, VIC-UCC (Universitat de Vic-Universitat Central de Catalunya), Barcelona, Spain

965 CCR5 Blockade With Maraviroc Does Not Prevent SIVmac Oral Transmission to Macaques

Egidio Brocca-Cofano[1]; Cuiling Xu[1]; Dongzhu Ma[1]; Benjamin Policicchio[1]; Kevin Raehtz[1]; Tammy Dunsmore[1]; George Richter-Haret[1]; Brandon F. Keele[2]; Ivona Pandrea[1]; Cristian Apetrei[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]National Cancer Institute (NCI), Frederick, MD, US

966LB Correlation of In Vivo Cabotegravir Concentration and Prevention of SIV in Macaques

William R. Spreen[4]; Anabel Lowry[1]; Ranajit Pal[2]; Yun Lan Yueh[4]; Susan Ford[4]; Nicola Richardson-Harman[3]; Jim A. Turpin[1]; Fulvia Veronese[1]; **James E. Cummins**[1]
ABL/BIOQUAL NHP Team

[1]National Institutes of Health, Bethesda, MD, US; [2]Advanced Bioscience Laboratories, Inc, Rockville, MD, US; [3]Alpha StatConsult LLC, Damascus, MD, US; [4]GlaxoSmithKline, Durham, NC, US

967 MZC Gel Inhibits Ex Vivo HIV-1 and HSV-2 Infection in Human Cervical Mucosa

Guillermo Villegas; Giulia Calenda; Patrick Barnable; Keith Levendosky; Michael Cooney; José Fernández-Romero; Thomas Zydowsky; Natalia Teleshova

Population Council, New York, NY, US

968 GRFT/Carrageenan Gel Inhibits SHIV-RT and HSV-2 Infection in Macaque Vaginal Mucosa

Giulia Calenda[1]; Patrick Barnable[1]; Keith Levendosky[1]; Kyle Kleinbeck[1]; Agegnehu Gettie[2]; James Blanchard[4]; José Fernández-Romero[1]; Barry O'Keefe[3]; Thomas Zydowsky[1]; Natalia Teleshova[1]

[1]Population Council, New York, NY, US; [2]Aaron Diamond AIDS Research Center, New York, NY, US; [3]National Cancer Institute (NCI), Fredrick, MD, US; [4]Tulane University, Covington, LA, US

TUESDAY, FEBRUARY 24, 2015

Session P-V3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

PrEP: Uptake

969 Sustained PrEP Use Among High-Risk African HIV Seroincident Couples Participating in a PrEP Demonstration Project

Renee Heffron[1]; Kenneth Ngure[2]; Nulu Bulya Semiyaga[3]; Josephine Odoyo[4]; Edna Tindimwebwa[5]; Jennifer Morton[1]; Lara Kidoguchi[1]; Mark A. Marzinke[6]; Connie Celum[1]; Jared Baeten[1]
Partners Demonstration Project Team

[1]University of Washington, Seattle, WA, US; [2]Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]Kenya Medical Research Institute, Nairobi, Kenya; [5]Kabwohe Clinic Research Center, Kabwohe, Uganda; [6]Johns Hopkins University School of Medicine, Baltimore, MD, US

970 PrEP Engagement for HIV Prevention: Results From the iPrEx Open Label Extension (OLE)

David V. Glidden[6]; Susan P. Buchbinder[1]; Peter L. Anderson[2]; Vanessa McMahan[3]; K. Rivet Amico[4]; Albert Liu[1]; Sybil Hosek[5]; Megha Mehrotra[6]; Robert M. Grant[3]
iPrEx Investigators

[1]San Francisco Department of Public Health, San Francisco, CA, US; [2]University of Colorado, Denver, CO, US; [3]Gladstone Institute, San Francisco, CA, US; [4]University of Michigan, Ann Arbor, MI, US; [5]John Stronger Hospital, Chicago, IL, US; [6]University of California San Francisco, San Francisco, CA, US

971 Preliminary Follow-up of Injecting Drug Users Receiving Preexposure Prophylaxis

Michael T. Martin[1]; Suphak Vanichseni[2]; Pravan Suntharasamai[2]; Udomsak Sangkum[2]; Philip Mock[1]; Manoj Leethochawalit[3]; Sithisat Chiamwongpaet[3]; Somyot Kittimunkong[4]; Marcel Curlin[1]; Kachit Choopanya[2]

[1]US Centers for Disease Control and Prevention (CDC), Nonthaburi, Thailand; [2]Bangkok Tenofovir Study Group, Bangkok, Thailand; [3]Bangkok Metropolitan Administration, Bangkok, Thailand; [4]Ministry of Public Health, Nonthaburi, Thailand

972 Recent Increases in PrEP Utilization at a Boston Community Health Center Among Men Who Have Sex With Men, 2011-2014: Transition From Research to Clinical Practice

Kenneth H. Mayer[1]; Kenneth Levine[1]; Chris Grasso[1]; Douglas S. Krakower[1]; Matthew Mimiaga[2]

[1]Fenway Health, Boston, MA, US; [2]Harvard School of Public Health, Boston, MA, US

973 Barriers to Effective Prevention: Applying a PrEP Care Continuum to a US Cohort of Black and White MSM

Colleen F. Kelley; Erin M. Kahle; Aaron Siegler; Carlos del Rio; Travis Sanchez; Patrick Sullivan; Eli S. Rosenberg

Emory University, Atlanta, GA, US

974 Provider Prescription of Preexposure Prophylaxis (PrEP) for HIV Infection

Shikha Garg; John Weiser; Linda Beer; Jacek Skarbinski

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Session P-V4 Poster Session — Poster Hall

2:30 pm – 4:00 pm

PrEP: Measures and Correlates of Adherence

975 Urine Assay for Tenofovir to Monitor Adherence to Tenofovir-Emtricitabine as PrEP

Helen C. Koenig[1]; Karam Mounzer[1]; **Giffin W. Daughtridge**[1]; Caroline E. Sloan[1]; Linden Lalley-Chareczko[2]; Ganesh Moorthy[3]; S. Caitlin Conyngham[2]; Elizabeth Ketner[1]; Luis J. Montaner[4]; Pablo Tebas[1]

[1]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, US; [2]Philadelphia FIGHT, Philadelphia, PA, US; [3]The Children's Hospital of Philadelphia, Philadelphia, PA, US; [4]Wistar Institute, Philadelphia, PA, US

976 Comparison of Adherence Measures in a Clinical Trial of Preexposure Prophylaxis

Davis C. Muganzi[1]; Jessica Haberer[2]; Yap Boum[1]; Nicholas Musinguzi[1]; Allan Ronald[4]; Connie Celum[3]; Jared Baeten[3]; David R. Bangsberg[4]

[1]Mbarara University of Science and Technology, Kampala, Uganda; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]University of Washington, Seattle, WA, US; [4]University of Manitoba, Winnipeg, Canada

977 Self-Reported Recent PrEP Use Has Strong Relation to Drug Detection in iPrEx OLE

Rivet Amico[1]; Vanessa McMahan[2]; Megha Mehrotra[2]; Peter L. Anderson[2]; Juan Guanira[2]; Valdilea Veloso[2]; Robert M. Grant[2]
the iPrEx study team

[1]University of Michigan, Ann Arbor, MI, US; [2]Gladstone Institute, San Fransicso, CA, US

978LB HPTN 067/ADAPT Cape Town: A Comparison of Daily and Nondaily PrEP Dosing in African Women

Linda-Gail Bekker[1]; james Hughes[2]; Rivet Amico[4]; Surita Roux[3]; Craig Hendrix[5]; Peter L. Anderson[6]; Bonnie Dye[7]; Vanessa Elharrar[8]; Michael J. Stirratt[9]; Robert Grant[10]

[1]Dept of Medicine and Institute of Infectious Disease and Molecular Medicine, Cape Town, South Africa; [2]HIV Prevention Trials Network, Seattle, WA, US; [3]The Desmond Tutu HIV Centre, Cape Town, South Africa; [4]University of Michigan, Ann Arbor, MI, US; [5]Johns Hopkins University, Baltimore, MD, US; [6]University of Colorado, Aurora, CO, US; [7]FHI360, Durham, NC, US; [8]PSP/DAIDS/NIAID/NIH, Bethesda, MD, US; [9]Center for Mental Health Research on AIDS, Bethesda, MD, US; [10]University of California, San Francisco, CA, US

979 Correlates of Early Adherence in VOICE PrEP Trial Differ Between Oral and Vaginal Products

Ariane van der Straten[1]; Elizabeth R. Brown[2]; James Dai[2]; Craig Hendrix[3]; Karen Liu[2]; Cynthia Grossman[4]; Z M. Chirenje[5]; Jeanne Marrazzo[6]

[1]RTI, San Francisco, CA, US; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]National Institute of Mental Health (NIMH), Bethesda, MD, US; [5]University of Zimbabwe–University of California San Francisco Research Collaboration, Harare, Zimbabwe; [6]University of Washington, Seattle, WA, US

980 Intimate Partner Violence Is Associated With Low PrEP Adherence in African Women

Sarah T. Roberts[1]; Connie Celum[1]; Nelly Mugo[3]; Jessica Haberer[2]; Craig R. Cohen[4]; Elizabeth Irungu[5]; James N. Kiarie[6]; Edwin Were[7]; Jared Baeten[1]
On behalf of the Partners PrEP Study Team

[1]University of Washington, Seattle, WA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Kenya Medical Research Institute, Nairobi, Kenya; [4]University of California San Francisco, San Francisco, CA, US; [5]Kenyatta National Hospital, Nairobi, Kenya; [6]University of Nairobi, Nairobi, Kenya; [7]Moi University, Eldoret, Kenya

WEDNESDAY, FEBRUARY 25, 2015

Session P-V5 Poster Session — Poster Hall

2:30 pm – 4:00 pm

PrEP: Evaluating Potential Harm

981 Reversibility of Kidney Function Decline in HIV-1–Uninfected Men and Women Using Preexposure Prophylaxis

Kenneth K. Mugwanya[1]; Christina Wyatt[2]; Connie Celum[1]; Deborah Donnell[3]; Nelly Mugo[4]; James N. Kiarie[5]; Allan Ronald[6]; Jared Baeten[1]
On behalf of the Partners PrEP Study Team

[1]University of Washington, Seattle, WA, US; [2]Mount Sinai School of Medicine, New York, NY, US; [3]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [4]Kenya Medical Research Institute, Nairobi, Kenya; [5]University of Nairobi, Nairobi, Kenya; [6]University of Manitoba, Winnipeg, Canada

982 Minor Drug-Resistant Variants Infrequently Detected in Seroconverters From MTN 003 (VOICE)

Constantinos Panousis[1]; Elias K. Halvas[1]; Cliff Kelly[2]; Jeanne Marrazzo[3]; Z M. Chirenje[4]; John W. Mellors[1]; **Urvi M. Parikh**[1]
On behalf of the MTN 003 Protocol Team

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [3]University of Washington, Seattle, WA, US; [4]UZ-UCSF Collaborative Research Programme, Harare, Zimbabwe

983 PrEP-Selected Drug Resistance Fades by Six Months Following Drug Cessation

Julie F. Weis[1]; Jared Baeten[2]; Ruth Kanthula[3]; Connor McCoy[1]; Lisa Frenkel[2]; Nelly Mugo[2]; Frederick Matsen[1]; Julie M. Overbaugh[1]; Connie Celum[2]; Dara A. Lehman[1]

[1]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [2]University of Washington, Seattle, WA, US; [3]Seattle Children's Research Institute, Seattle, WA, US; [4]Fred Hutchinson Cancer Research Center, Seattle, WA, US

984 Randomized Controlled Trial on ART Outcomes in Tenofovir Gel Trial Seroconvertors

Anushka Naidoo; Nivashnee Naicker; Lise Werner; Nigel Garrett; Sarah Dlamini; Villeshni Asari; Nelisile Majola; Cheryl Baxter; Quarraisha Abdool Karim; Salim S. Abdool Karim

Center for the AIDS Program of Research in South Africa, Durban, South Africa

985 Frequent Dapivirine Cross-Resistance of HIV from 1st-line ART Failures in S. Africa

Kerri J. Penrose[1]; Kristen A. Hamanishi[1]; Kelley C. Gordon[1]; Raquel V. Viana[2]; Carole L. Wallis[3]; John W. Mellors[1]; Urvi M. Parikh[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]Lancet Laboratories, Johannesburg, South Africa; [3]Lancet Laboratories/BARC-SA, Johannesburg, South Africa

986 Effect of TDF Monotherapy PrEP on Immune Function in Seroconverting Individuals

Marcel E. Curlin[1]; Michael T. Martin[1]; Punneeporn Wasinrapee[2]; Wanna Leelawiwat[2]; Boonyos Raengsakulrach[2]; Janet McNicholl[1]; Pravan Suntharasamai[3]; Udomsak Sangkum[3]; Suphak Vanichseni[3]; Kachit Choopanya[3]

[1]US Centers for Disease Control and Prevention (CDC), Apo, US; [2]Thailand Ministry of Public Health-Centers for Disease Control and Prevention Collaboration, Nothaburi, Thailand; [3]Bangkok Tenofovir Study Group, Bangkok, Thailand

987 The Impact of Preexposure Prophylaxis on Antibody Maturation in HIV-Infected Women

Oliver B. Laeyendecker[1]; Andrew D. Redd[1]; Martha Nason[3]; Andrew Longosz[1]; Quarraisha Abdool Karim[2]; Vivek Naranbhai[2]; Nigel Garrett[2]; Salim S. Abdool Karim[2]; Thomas C. Quinn[1]

[1]National Institute of Allergy and Infectious Diseases, Baltimore, MD, US; [2]CAPRISA, University of KwaZulu-Natal, Congella, South Africa; [3]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

988 Medication Sharing Among African HIV Serodiscordant Couples Enrolled in a PrEP Trial

Kerry A. Thomson[1]; Jessica Haberer[4]; Connie Celum[1]; Andrew Mujugira[1]; Patrick Ndase[1]; Craig Hendrix[2]; Mark A. Marzinke[2]; Allan Ronald[3]; David Bangsberg[4]; Jared Baeten[1]
On behalf of the Partners PrEP Study Team

[1]University of Washington, Seattle, MA, US; [2]Johns Hopkins University, Baltimore, MD, US; [3]University of Manitoba, Winnipeg, Canada; [4]Massachusetts General Hospital, Boston, MA, US

THURSDAY, FEBRUARY 26, 2015

Session P-V6 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HIV Prevention, Miscellaneous

989 HIV-1 Transmission Risk Persists During the First 6 Months of Antiretroviral Therapy

Andrew Mujugira[1]; Katherine Thomas[1]; Connie Celum[1]; Deborah Donnell[2]; Carey Farquhar[1]; Elizabeth Bukusi[3]; Jared Baeten[1]
On behalf of the Partners PrEP Study Team

[1]University of Washington, Seattle, WA, US; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [3]Kenya Medical Research Institute, Nairobi, Kenya

990 Long-Term ART Outcomes in Botswana Encouraging Treatment as Prevention Approach

Hermann Bussmann[4]; William C. Wester[1]; Ernest Fetogang[2]; Tony Chebani[2]; Sikhulile Moyo[3]; Naledi M. Mlaudzi[2]; Erik V. Widenfelt[3]; Joseph Makhema[3]; Max Essex[4]; Richard Marlink[4]

[1]Vanderbilt University School of Medicine, Nahville, TN, US; [2]Ministry of Health, Gaborone, Botswana; [3]Botswana Harvard AIDS Institute Partnership for HIV Research and Education, Gaborone, Botswana; [4]Harvard School of Public Health, Boston, MA, US

991LB Use of Population Viral Load to Predict HIV-Incidence in a Hyperendemic Population in Rural KwaZulu-Natal, South Africa

Frank Tanser[3]; Tulio de Oliveira[3]; Till Barnighausen[2]; Deenan Pillay[1]

[1]University College London, London, United Kingdom; [2]Harvard School of Public Health, Boston, MA, US; [3]University of KwaZulu-Natal, Mtubatuba, South Africa

992LB Phase 1 Safety & PK Trial of Polyurethane Tenofovir Disoproxil Fumarate Vaginal Ring

Marla J. Keller[1]; Pedro Mesquita[1]; Mark A. Marzinke[2]; Ryan Teller[3]; Bruce Frank[4]; Mark Mitchnick[4]; Peter L. Anderson[5]; Craig Hendrix[2]; Patrick F. Kiser[3]; Betsy Herold[1]

[1]Albert Einstein College of Medicine, Bronx, NY, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]Northwestern University, Evanston, IL, US; [4]Particle Sciences, Inc, Bethlehem, PA, US; [5]University of Colorado, Aurora, CO, US

993 Investigating the Pharmacokinetics of Rectal 1% Tenofovir Gel in Rhesus Macaques

Charles W. Dobard[1]; Andrew Taylor[1]; Chuong Dinh[1]; Chou-Pong Pau[1]; Ian McGowan[2]; Lisa Rohan[2]; Walid Heneine[1]

[1]Centers for Disease Control and Prevention, Atlanta, GA, USA, Atlanta, GA, US; [2]University of Pittsburgh Magee-Womens Research Institute, Pittsburgh, PA, US

994 CHARM-01, a Phase 1 Rectal Safety, Acceptability, PK/PD Study of 3 Tenofovir Gels

Ian McGowan[1]; Kathy Duffill[2]; Charlene Dezzutti[1]; Nicola Richardson-Harman[3]; Mark A. Marzinke[4]; Ross D. Cranston[1]; Lisa Rohan[1]; Craig W. Hendrix[4]; Julie Elliott[5]; Peter Anton[5]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]Magee-Womens Research Institute, Pittsburgh, PA, US; [3]Alpha StatConsult LLC, Damascus, MD, US; [4]Johns Hopkins University School of Medicine, Baltimore, MD, US; [5]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US

995 Female Condom Functionality in the Presence of a Vaginal Ring

Annalene M. Nel[1]; Mildie Leuvennink[1]; Neliette Van Niekerk[1]; Terri Walsh[2]; Ron Frezieres[2]

[1]International Partnership for Microbicides, Paarl, South Africa; [2]California Family Health Council Inc, Los Angeles, CA, US

TUESDAY, FEBRUARY 24, 2015

Session P-W1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HIV Testing and the Continuum of Care in the Industrialized World

996 Continuous Retention Predicts Viral Suppression Across the US and Canada

Peter F. Rebeiro[1]; Baligh R. Yehia[2]; Kelly Gebo[3]; Bryan Lau[3]; Kenneth H. Mayer[4]; Michael A. Horberg[5]; Mari Kitahata[6]; John Gill[7]; Timothy Sterling[1]; Stephen J. Gange[3]
North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)

[1]Vanderbilt University, Nashville, TN, US; [2]University of Pennsylvania, Philadelphia, PA, US; [3]Johns Hopkins University, Baltimore, MD, US; [4]Harvard University, Boston, MA, US; [5]Mid-Atlantic Permanente Research Institute, Kaiser Permanente Mid-Atlantic States, Rockville, MD, US; [6]University of Washington, Seattle, WA, US; [7]University of Calgary, Alberta Health Services, Calgary, Canada

997 Disparities in HIV Viral-Load Suppression Among MSM, the HIV Outpatient Study, 2013

Kate Buchacz[1]; Carl Armon[2]; Ellen Tedaldi[3]; Frank J. Palella[4]; Richard Novak[5]; Doug Ward[6]; Benjamin Young[7]; Rachel Debes[2]; Marcus Durham[1]; John T. Brooks[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]Cerner Corporation, Vienna, VA, US; [3]Temple University School of Medicine, Philadelphia, PA, US; [4]Northwestern University, Chicago, IL, US; [5]University of Illinois at Chicago, Chicago, IL, US; [6]Dupont Circle Physicians Group, Washington, DC, US; [7]International Association of Providers in AIDS Care, Washington, DC, US

998 Early Linkage to HIV Care and Antiretroviral Therapy Use Among People Who Inject Drugs: 20 US Cities, 2009 and 2012

Brooke Hoots; Teresa Finlayson; Dita Broz; Gabriela Paz-Bailey

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

999 Late HIV Diagnosis in Metropolitan Areas of the United States and Puerto Rico

H. Irene Hall[1]; Tian Tang[2]; Lorena Espinoza[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]ICF International, Atlanta, GA, US

1000 HIV Care During the Last Year of Life

H. Irene Hall[1]; Lorena Espinoza[1]; Shericka Harris[2]; Jing Shi[2]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]ICF International, Atlanta, GA, US

1001 Reductions in the Time From HIV Infection to ART Initiation in New York City

Sarah L. Braunstein[1]; McKaylee Robertson[2]; Julie Myers[1]; Bisrat Abraham[3]; Denis Nash[4]

[1]New York City Department of Health and Mental Hygiene, Queens, NY, US; [2]City University of New York, New York, NY, US; [3]Weill Cornell Medical College, New York, NY, US; [4]City University of New York School of Public Health, New York, NY, US

1002 Return to HIV-Related Medical Care After a Hiatus of ≥1 Year, New York State, 2013

Carol-Ann Swain[4]; Daniel Gordon[4]; Jessica L. Simpson[3]; Bridget J. Anderson[4]; Bruce D. Agins[1]; Lou C. Smith[2]

[1]Office of the Medical Director, New York State Department of Health, New York, NY, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [3]Division of Epidemiology, Evaluation and Research, New York State Department of Health, Albany, NY, US; [4]New York State Department of Health, Albany, NY, US

1003 Care-Cascade Status of Partners of Persons With New HIV Infections in North Carolina

Anna B. Cope[1]; Lisa Hightow-Weidman[1]; JoAnn D. Kuruc[1]; Jenni Marmorino[1]; Steve Beagle[1]; Philip J. Peters[2]; Cynthia L. Gay[1]

[1]University of North Carolina, Chapel Hill, NC, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

1004 The Role of HIV Status Disclosure in Retention in Care and Viral-Load Suppression

Latesha E. Elopre; Andrew Westfall; Michael J. Mugavero; Anne Zinski; Greer Burkholder; Edward Hook; Nicholas Van Wagoner

University of Alabama at Birmingham, Birmingham, AL, US

1005 Alcohol and Substance Use and Timing of Presentation to HIV Care Across the United States

Jesse Abbott Klafter[1]; Daniel R. Drozd[3]; Michael J. Mugavero[2]; Katerina Christopoulos[4]; Christopher W. Mathews[7]; Joseph J. Eron[8]; Kenneth H. Mayer[6]; Matthew Mimiaga[5]; Mari Kitahata[3]; Heidi M. Crane[3]
Center for AIDS Research Network of Integrated Clinical Systems (CNICS)

[1]University of Washington, Seattle, WA, US; [2]University of Alabama at Birmingham, Birmingham, AL, US; [3]University of Washington, Seattle, WA, US; [4]University of California San Francisco, San Francisco, CA, US; [5]Harvard Medical School, Boston, MA, US; [6]Fenway Health, Boston, MA, US; [7]University of California San Diego (UCSD), San Diego, CA, US; [8]University of North Carolina, Chapel Hill, NC, US

1006 Marijuana Use and Its Nuanced Relationship With HIV Treatment Continuum Metrics

John A. Schneider[1]; Ethan Morgan[1]; Stuart Michaels[2]; Britt Skaathun[1]; Lindsay Young[1]; Robert W. Coombs[3]; Phil Schumm[1]; Dexter Voisin[1]; Sam Friedman[4]
UConnect Study Team

[1]University of Chicago, Chicago, IL, US; [2]NORC, Chicago, IL, US; [3]University of Washington, Seattle, WA, US; [4]National Development Research Institute, New York, NY, US

1007 "Test-and-Treat" in the Netherlands

Ard van Sighem[1]; Luuk Gras[1]; Eline Op de Coul[2]; Daniela Bezemer[1]; Michiel van Agtmael[3]; Godelieve de Bree[4]; Peter Reiss[1]
On behalf of the ATHENA National Observational HIV Cohort

[1]Stichting HIV Monitoring, Amsterdam, Netherlands; [2]National Institute for Public Health and the Environment, Bilthoven, Netherlands; [3]VU University Medical Centre, Amsterdam, Netherlands; [4]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands

1008 Estimates of HIV Prevalence, Proportion of Diagnosed Patients and Quality of Treatment in Switzerland

Philipp Kohler[2]; Axel J. Schmidt[3]; Bruno Ledergerber[2]; **Pietro L. Vernazza**[1]

[1]Cantonal Hospital St. Gallen, St. Gallen, Switzerland; [2]Universitätsspital Zürich, Zurich, Switzerland; [3]Federal Office of Public Health, Bern, Switzerland

1009 Medical Care Interruptions in HIV-infected Patients: Characteristics and Consequences

Lise Cuzin[1]; Pierre Dellamonica[2]; Yazdan Yazdanpanah[7]; Sabelline Bouchez[3]; David Rey[6]; Bruno Hoen[5]; André Cabié[4]

[1]Toulouse University Hospital, Toulouse, France; [2]University Hospital, Nice, Nice, France; [3]University Hospital, Nantes, France; [4]University Hospital, Fort de France, France; [5]University Hospital, Pointe à Pitre, France; [6]University Hospital, Strasbourg, France; [7]Hôpital Bichat-Claude Bernard, APHM, Paris, France

1010 Blood Donor Test-Seeking Motivation and Prior HIV Testing Experiences in São Paulo

Hong-Ha M. Truong[1]; Paula Blatyta[2]; Sandra Montebello[2]; Sandra Esposti[2]; Fatima Hangai[2]; Nanci Salles[2]; Alfredo Mendrone[2]; Ester C. Sabino[3]; Willi McFarland[4]; Thelma T. Gonçalez[5]

[1]University of California San Francisco, San Francisco, CA, US; [2]Fundação Pró-Sangue/ Hemocentro de São Paulo, São Paulo, Brazil; [3]University of São Paulo, São Paulo, Brazil; [4]San Francisco Department of Public Health, San Francisco, CA, US; [5]Blood Systems Research Institute/University of California San Francisco, San Francisco, CA, US

Session P-W2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HIV Testing and the Continuum of Care in the Developing World

1011 Treatment Interruptions in ART Programmes in Resource-Limited Settings: 2003 to 2013

Gail B. Cross[1]; Tim Spelman[2]; Daniel P. O'Brien[4]; Nathan Ford[3]; Jane Greig[4]; James H. McMahon[1]

[1]Monash University/Alfred Hospital, Prahan, Australia; [2]Burnet Institute, Melbourne, Australia; [3]World Health Organization (WHO), Geneva, Switzerland; [4]Médecins Sans Frontières, London, United Kingdom

1012 Time to ART Qualification and Retention Among Patients With Early HIV in Haiti

Rita T. Dadaille[1]; Serena P. Koenig[1]; Kelley Henessey[2]; Ellie Cooper[2]; Pierre Cremieux[2]; William J. Pape[1]
Analysis Group; Les Centres GHESKIO IT Team

[1]Gheskio Centers, Port au Prince, Haiti; [2]Analysis Group, Boston, MA, US

1013 Awareness of HIV Diagnosis in the Swaziland HIV Incidence Measurement Survey

Tanya M. Ellman[1]; Ruth Emerson[4]; Deborah Donnell[4]; Neena M. Philip[1]; Rejoice Nkambule[2]; Naomi Bock[3]; Peter Ehrenkranz[5]; George Bicego[3]; Jessica E. Justman[1]

[1]ICAP at Columbia University, New York, NY, US; [2]Ministry of Health, Mbabane, Swaziland; [3]US Centers for Disease Control and Prevention, Atlanta, GA, US; [4]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [5]Centers for Disease Control and Prevention, Mbabane, Swaziland

1014 Who Is at Risk of Being Untested and Unaware of HIV-Positive Status in KwaZulu-Natal?

Helena Huerga[1]; Gilles Van Cutsem[2]; Jihane Ben Farhat[1]; Malika Bouhenia[1]; Matthew Reid[2]; David Maman[1]; Jean-François Etard[1]; Thomas Ellman[2]

[1]Epicentre, Paris, France; [2]Médecins Sans Frontières, Cape Town, South Africa

1015 Impact of Unplanned Care Interruption on Immune Recovery After ART Initiation in Nigeria

Aimalohi A. Ahonkhai[1]; Juliet Adeola[2]; Bolanle Banigbe[2]; Ifeyinwa Onwuatuelo[2]; Ingrid V. Bassett[1]; Elena Losina[3]; Kenneth A. Freedberg[1]; Prosper Okonkwo[2]; Susan Regan[1]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]AIDS Prevention Initiative Nigeria, Jabi District, Nigeria; [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US

1016 Linkage to HIV Care Among Men Who Have Sex With Men and Drug Users in India: Getting to 90

Sunil S. Solomon[1]; Allison M. McFall[2]; Aylur K. Srikrishnan[3]; Gregory M. Lucas[1]; Canjeeveram K. Vasudevan[3]; David D. Celentano[2]; Muniratnam S. Kumar[3]; Suniti Solomon[3]; Shruti H. Mehta[2]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]YR Gaitonde Centre for AIDS Research and Education, Chennai, India

WEDNESDAY, FEBRUARY 25, 2015

Session P-W3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Risk Factors for Transmission in MSM

1017 Sex Pro: A Personalized HIV Risk Assessment Tool for Men Who Have Sex With Men

Hyman Scott[1]; Eric Vittinghoff[2]; Risha Irving[3]; Albert Liu[1]; Sheldon D. Fields[5]; Manya Magnus[6]; Darrell P. Wheeler[7]; Kenneth H. Mayer[4]; Beryl A. Koblin[8]; Susan P. Buchbinder[1]

[1]San Francisco Department of Public Health, San Francisco, CA, US; [2]University of California San Francisco, San Francisco, CA, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]Fenway Health, Boston, MA, US; [5]Florida International University, Miami, FL, US; [6]George Washington University, Washington, DC, US; [7]Loyola University Chicago, Chicago, IL, US; [8]New York Blood Center, New York, NY, US

1018 Unreported Sexual Risk Behavior Among MSM Newly Diagnosed With HIV Infection

Hsiu Wu[1]; Lisa B. Hightow-Weidman[2]; Cindy L. Gay[2]; Tonyka Jackson[3]; Emily Pike[2]; Jenni Marmorino[2]; Steve Beagle[2]; Laura Hall[3]; Philip J. Peters[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]ICF International, Atlanta, GA, US

1019LB HIV Transmission in Male Serodiscordant Couples in Australia, Thailand and Brazil

Andrew E. Grulich[1]; Benjamin R. Bavinton[1]; Fengyi Jin[1]; Garrett Prestage[1]; Iryna B. Zablotska[1]; Beatriz Grinsztejn[2]; Nittaya Phanuphak[3]; Richard Moore[4]; Kersten K. Koelsch[1]
On behalf of the Opposites Attract Study Group

[1]University of New South Wales, Sydney, Australia; [2]Instituto de Pesquisa Clínica Evandro Chagas, Rio de Janiero, Brazil; [3]Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [4]Northside Clinic, Melbourne, Australia

1020 Seminal Shedding of CMV and HIV Transmission Among Men Who Have Sex With Men

Sara Gianella Weibel[1]; Konrad Scheffler[1]; Sanjay Mehta[1]; Susan J. Little[1]; Lorri Freitas[2]; Sheldon R. Morris[1]; David M. Smith[1]

[1]University of California San Diego, La Jolla, CA, US; [2]County of San Diego Public Health Services, San Diego, CA, US

1021 Risk Factors for Acute and Early HIV Infection Among MSM in San Diego, 2008–2014

Martin Hoenigl; Christy M. Anderson; Sanjay Mehta; Nella L. Green; Davey M. Smith; Susan Little

University of California San Diego, San Diego, CA, US

1022 Influence of Voluntary Repeat HIV Testing on Sexual Risk Behavior Among MSM

Martin Hoenigl; Davey M. Smith; Christy M. Anderson; Nella L. Green; Sanjay Mehta; Susan J. Little

University of California San Diego, San Diego, CA, US

1023 HIV-Positive MSM With Unsuppressed Viral Load Are More Likely to Engage in Risky Sex: Vancouver, Canada

David Moore[1]; Zishan Cui[1]; Nathan J. Lachowsky[1]; Henry F. Raymond[2]; Eric Roth[3]; Asheligh Rich[1]; Paul Sereda[1]; Julio Montaner[1]; Mark Gilbert[4]; Robert Hogg[1]

[1]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; [2]San Francisco Department of Public Health, San Francisco, CA, US; [3]University of Victoria, Victoria, Canada; [4]BC Centre for Disease Control, Vancouver, Canada

1024 Substance Use, Mental Health, and HIV Risk Behavior Among MSM in Vancouver, Canada

Nathan J. Lachowsky[1]; Zishan Cui[2]; Asheligh Rich[2]; Paul Sereda[2]; Thomas L. Patterson[3]; Trevor Corneil[1]; Mark Gilbert[4]; Eric Roth[5]; Robert Hogg[6]; David Moore[1]

[1]University of British Columbia, Vancouver, Canada; [2]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; [3]University of California San Diego, San Diego, CA, US; [4]Ontario HIV Treatment Network, Toronto, Canada; [5]University of Victoria, Victoria, Canada; [6]Simon Fraser University, Burnaby, Canada

1025 Electronic and Online Innovations in Respondent-Driven Sampling Methodology

Nathan J. Lachowsky[1]; Allan Lal[2]; Zishan Cui[2]; Asheligh Rich[2]; Paul Sereda[2]; Henry Fisher Raymond[3]; Jamie I. Forrest[1]; Eric Roth[4]; Robert Hogg[2]; David Moore[1]

[1]University of British Columbia, Vancouver, Canada; [2]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada; [3]University of California San Francisco, San Francisco, CA, US; [4]University of Victoria, Victoria, Canada

1026 Incident Symptomatic Gonorrhea Infection Among Men Who Have Sex With Men, Thailand

Marcel E. Curlin[1]; Sarika Pattanasin[1]; Pikunchai Luechai[1]; Anuwat Sriporn[1]; Jaray Tongtoyai[1]; Eileen F. Dunne[1]; Wichuda Sukwicha[1]; Oranuch Kongpechsatit[1]; Pachara Sirivongrangson[2]; Timothy Holtz[1]

[1]US Centers for Disease Control and Prevention (CDC), Apo, US; [2]Thai Ministry of Public Health, Nonthaburi, Thailand

Session P-W4 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Transmission Through Needles and Heterosexual Contact

1027 Occupationally Acquired HIV Infection by Healthcare Personnel–United States, 1985-2013

M Patricia Joyce; David Kuhar; John T. Brooks

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

1028 Analyzing Trends in HIV Risks for Injection Drug Users by Respondent-Driven Sampling

Kathleen A. Brady; Tanner B. Nassau; Jennifer Shinefeld; Catherine Mezzacappa

Philadelphia Department of Public Health, Philadelphia, PA, US

1029 Sexual Transmission of HIV and Possible Underreporting of Drug Use in Kazakhstan

Anna Deryabina; Padmaja Patnaik; Charon Gwynn; Wafaa M. El-Sadr

ICAP at Columbia University, Almaty, Kazakhstan

1030 Can We Trust Self-Reported Condom Use? Association Between Reporting Bias and STIs

Hongjie Liu

University of Maryland, College Park, College Park, MD, US

1031 Prevalence and Correlates of Exchange Sex Among Low-Income Heterosexual Women in 21 US Cities

Catlainn Sionean; Rashunda Lewis; Lina M. Nerlander; Gabriela Paz-Bailey
On behalf of the NHBS Study Group

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

1032 HIV and STIs Among Transgendered Populations: Four Country Survey From Central America

David Ham[1]; Sanny Y. Northbrook[2]; Sonia Morales-Miranda[3]; Maria Elena Guardado[4]; Mary Kamb[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]CDC Central America Region, Guatemala City, Guatemala; [3]HIV Unit of Center for Health Studies, Del Valle University of Guatemala, Guatemala City, Guatemala; [4]TEPHINET/ The Taskforce for Global Health Inc., Guatemala City, Guatemala

1033 Incidence of Curable Sexually Transmitted Infections Among South African Women Recently Infected With HIV

Jennifer E. Balkus[1]; Marla E. Husnik[1]; Thesla Palanee-Phillips[2]; Ravindre Panchia[3]; Ishana Harkoo[4]; Arendevi Pather[5]; Vaneshree Govender[5]; Marthinette Taljaard[6]; Pamina Gorbach[7]; Sharon Riddler[8]

[1]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [2]University of the Witwatersrand, Johannesburg, South Africa; [3]Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa; [4]CAPRISA/University of KwaZulu-Natal, Durban, South Africa; [5]Medical Research Council, Durban, South Africa; [6]The Aurum Institute, Klerksdorp, South Africa; [7]University of California Los Angeles, Los Angeles, CA, US; [8]University of Pittsburgh, Pittsburgh, PA, US

1034 Population Mobility, Sexual Behavior and Risk of HIV Infection in Sub-Saharan Africa

Laurence Palk; Sally Blower
On behalf of the Center for Biomedical Modeling

David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US

1035 HIV Transmission Linkage Among Seroconverting Partners in HIV-Discordant Relationships in Kenya

Bhavna H. Chohan[1]; Brandon L. Guthrie[2]; Brian Khasimwa[4]; Stephanie Rainwater[3]; Barbara Lohman-Payne[2]; Rose Bosire[2]; Romel D. Mackelprang[2]; Julie M. Overbaugh[3]; Carey Farquhar[2]

[1]Kenya Medical Research Institute, Nairobi, Kenya; [2]University of Washington, Seattle, WA, US; [3]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [4]University of Nairobi, Nairobi, Kenya

1036 Rising School Enrollment & Declining HIV Risk, 15-19y, Rakai, Uganda, 1994-2013

John Santelli[1]; Sanyukta Mathur[1]; Xiao Yu Song[2]; Tzu-Jung Huang[2]; Ying Wei[2]; Tom Lutalo[3]; Fred Nalugoda[3]; Ronald H. Gray[4]; David Serwadda[3]

[1]New York–Presbyterian University Hospital of Columbia and Cornell, New York City, NY, US; [2]Columbia University–Mailman School of Public Health, New York, NY, US; [3]Rakai Health Sciences Program, Entebbe, Uganda; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

1037 Alcohol Use and HIV Risk Factors: Results From the 2011 Uganda AIDS Indicator Survey

George Aluzimbi

CDC Center for Global Health, Division of Global AIDS/HIV, Kampala, Uganda

1038 Population Attributable Fraction of HIV Due to Alcohol in Fishing Communities, Uganda

Noah Kiwanuka[5]; Ismail Ssekandi[2]; Ali Ssetaala[2]; Annet Nalutaaya[2]; Juliet Mpendo[2]; Paul K. Kitandwe[2]; Jan D. Bont[3]; Pontiano Kaleebu[4]; Nelson K. Sewankambo[5]

[1]Makerere University College of Health Sciences, Kampala, Uganda; [2]UVRI-IAVI HIV Vaccine Program, Entebbe, Uganda; [3]International AIDS Vaccine Initiative, New York, NY, US; [4]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda; [5]Makerere University College of Health Sciences, Kampala, Uganda

1039 Risky Sexual Behavior and HIV Infection Among Fisher Folk: Lake Kyoga Region, Uganda

Rose Apondi[1]; Rhoda Wanyenze[2]; Herbert S. Kiyingi[2]; Abdu-Maliki Muyinda[2]; Elizabeth Meassick[1]; Joy Kusiima[2]; David Serwadda[2]

[1]CDC Center for Global Health, Division of Global AIDS/HIV, Kampala, Uganda; [2]Makerere University School of Public Health, Kampala, Uganda

THURSDAY, FEBRUARY 26, 2015

Session P-W5 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Incidence and Prevalence of HIV Infection, Including Acute HIV

1040 Increases in HIV Diagnoses Among MSM in Metropolitan Statistical Areas, United States, 2003–2012

Lorena Espinoza; H. Irene Hall; Tian Tang; Anna Satcher Johnson; Amy Lansky

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

1041 Disparities in HIV by Race and Age Among Men Who Have Sex With Men, 20 US Cities

Cyprian Wejnert; Kristen Hess; Chuck E. Rose; **Alexandra B. Balaji**; Justin C. Smith; Gabriela Paz-Bailey
On behalf of the NHBS Study Group

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

1042 HIV Incidence Estimates, Introducing the Limiting Antigen Avidity EIA to Existing HIV Surveillance in Kiev City, Ukraine: 2013–2014

Ruth Simmons[1]; Ruslan Malyuta[2]; Nelli Chentsova[3]; Iryna Karnets[3]; Gary Murphy[4]; Antonia Medoeva[3]; Yuri Kruglov[5]; Alexander Yurchenko[3]; Kholoud Porter[1]; Andrew Copas[1]

[1]Medical Research Council at University College London, London, United Kingdom; [2]Perinatal Prevention of AIDS Initiative, Odessa, Ukraine; [3]Kyiv City AIDS Centre, Kyiv City, Ukraine; [4]Public Health England, London, United Kingdom; [5]Institute of Epidemiology, Kyiv, Ukraine

1043 Detection of Acute HIV Infection, US National HIV Surveillance System, 2008–2012

Laurie Linley; Qian An; Kristen Mahle Gray; Alexandra Oster; Angela L. Hernandez

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

1044 Differences in Acute Retroviral Syndrome by HIV-1 Subtype in a Multicentre Cohort Study in Africa

Eduard J. Sanders[1]; Kimberly A. Powers[2]; Etienne Karita[3]; Anatoli Kamali[4]; William Kilembe[5]; Susan Allen[6]; Eric Hunter[6]; Omu Anzala[7]; Pat Fast[8]; Matthew Price[8]

[1]KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya; [2]University of North Carolina, Chapel Hill, NC, US; [3]Project San Francisco, Kigali, Rwanda; [4]Medical Research Council/ Uganda Virus Research Institute, Entebbe, Uganda; [5]Zambia Emory Research Project, Lusaka, Zambia; [6]Emory University, Atlanta, GA, US; [7]Kenya AIDS Vaccine Initiative, Nairobi, Kenya; [8]International AIDS Vaccine Initiative,, New York, NY, US

1045 Using GPS Data to Construct a Spatial Map of the HIV Epidemic in Malawi

Danielle E. Robbins; Brian J. Coburn; Sally Blower

David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US

1046 HIV Incidence in Rural Malawi During Widespread Antiretroviral Treatment Availability

Alison Price[1]; Menard Chihana[2]; Ndoliwe Kayuni[2]; Amelia C. Crampin[1]; Milly Marston[1]; Basia Zaba[1]; Estelle McLean[1]; Olivier Koole[1]; Moffat Nyirenda[1]

[1]London School of Hygiene and Tropical Medicine, Chilumba, Malawi; [2]Karonga Prevention Study, Chilumba, Malawi

1047 HIV-1 Incidence Among Adult STI Clinic Patients in Blantyre, Malawi

Fatima Zulu[1]; Isaac Singini[1]; Newton I. Kumwenda[1]; Johnstone Kumwenda[1]; Sufia Dadabhai[2]

[1]Johns Hopkins University Research Project, Blantyre, Malawi; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

Session P-W6 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Disease Progression, Morbidity, and Mortality

1048 CD4 Cell Dynamics in HIV-1 Infection Before and After ART: Overview and Determinants

Anne Cori[1]; Mike Pickles[1]; Ard van Sighem[2]; Luuk Gras[2]; Daniela Bezemer[2]; Peter Reiss[2]; Christophe Fraser[1]
On behalf of the ATHENA Observational Cohort

[1]Imperial College London, London, United Kingdom; [2]HIV Monitoring Foundation, Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands

1049 IL-6 Partially Mediates the Effect of HIV Status on Survival

Kaku So-Armah[1]; Amy Justice[2]; David Rimland[3]; Maria Rodriguez-Barradas[4]; Adeel A. Butt[5]; David Leaf[6]; Russell Tracy[7]; Mohammad Sajadi[8]; Cynthia Gibert[9]; Matthew S. Freiberg[10]

[1]Yale University School of Medicine, New Haven, CT, US; [2]VA Connecticut Healthcare System, West Haven, CT, US; [3]Veterans Affairs Medical Center, Atlanta, GA, US; [4]Veterans Affairs Medical Center, Houston, TX, US; [5]Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates; [6]Veterans Affairs Medical Center, Greater Los Angeles, CA, US; [7]University of Vermont, Burlington, VT, US; [8]Veterans Affairs Medical Center, Baltimore, MD, US; [9]Veterans Affairs Medical Center, Washington, DC, US; [10]Vanderbilt University School of Medicine, Nashville, TN, US

1050 Persistently Elevated Macrophage Activation in HIV+ Women Reporting Heavy Alcohol Use

Seema N. Desai[1]; Kathleen M. Weber[2]; Jane Burke-Miller[3]; Audrey L. French[2]; Monica Gandhi[4]; Mark H. Kuniholm[5]; Elizabeth T. Golub[6]; Kendall Bryant[7]; Alan Landay[1]; Mardge Cohen[8]

[1]Rush University Medical Center, Chicago, IL, US; [2]CORE Center/Stroger Hospital of Cook County, Chicago, IL, US; [3]Hektoen Institute of Medicine, Chicago, IL, US; [4]University of California San Francisco, San Francisco, CA, US; [5]Albert Einstein College of Medicine, Bronx, NY, US; [6]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [7]National Institutes of Health/ National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, US; [8]Stroger Hospital of Cook County, Chicago, IL, US

1051 Is Survival Following HIV Seroconversion Still Improving, 17 Years After the Introduction of cART?

Ashley Olson[1]; Caroline Sabin[1]; Maria Prins[2]; Laurence Meyer[3]; Julia del Amo[4]; Genevieve Chene[5]; Osamah Hamouda[6]; Giota Touloumi[7]; Kholoud Porter[1]
On behalf of the CASCADE Collaboration in EuroCoord

[1]University College London, London, United Kingdom; [2]Public Health Service of Amsterdam, Amsterdam, Netherlands; [3]Inserm, Paris, France; [4]Instituto de Salud Carlos III, Madrid, Spain; [5]Inserm, Bordeaux, France; [6]Robert Koch Institute, Berlin, Germany; [7]University of Athens, Athens, Greece

1052 National Estimates of Life Expectancy After HIV Diagnosis: US HIV Surveillance Data

Azfar-e-Alam Siddiqi; H. Irene Hall; Xiaohong Hu; Ruiguang Song

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

1053 Age-Related Morbidities Among HIV-Infected Adults From 2000 to 2010

Cherise Wong[1]; Stephen J. Gange[1]; Michael A. Horberg[2]; Gregory D. Kirk[1]; Anita Rachlis[3]; John Gill[4]; Jennifer E. Thorne[1]; Robert Hogg[5]; James J. Goedert[6]; **Keri N. Althoff**[1]

[1]Johns Hopkins University, Baltimore, MD, US; [2]Mid-Atlantic Permanente Research Institute, Rockville, MD, US; [3]University of Toronto Sunnybrook Research Institute, Toronto, Canada; [4]University of Calgary, Alberta Health Services, Calgary, Canada; [5]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada; [6]National Cancer Institute (NCI), Rockville, MD, US

1054 A Retrospective Population-Based Examination of Prescription Drug Usage Prior to HIV Diagnosis Among HIV Cases and Their Controls: The Missed Opportunity for Diagnoses Epidemiological Study (MODES)

Souradet Y. Shaw[1]; Laurie Ireland[2]; Tara Carnochan[2]; Nancy Yu[1]; Carla Ens[3]; Yoav Keynan[1]; Ken Kasper[4]; Marissa Becker[1]
On behalf of the MODES Manitoba Team

[1]University of Manitoba, Winnipeg, Canada; [2]Nine Circles Community Health Centre, Winnipeg, Canada; [3]Manitoba Health, Winnipeg, Canada; [4]Manitoba HIV Program, Winnipeg, Canada

1055 Elevated Rates of Injury Among HIV-Positive Individuals in British Columbia

Hasina Samji[1]; Dmitry Shopin[1]; Wendy Zhang[1]; Oghenowede Eyawo[1]; Guillaume Colley[1]; Mark Hull[1]; Julio Montaner[3]; Robert Hogg[2]
On behalf of the COAST Study

[1]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; [2]Simon Fraser University, Burnaby, Canada; [3]University of British Columbia, Vancouver, Canada

1056 Higher Economic Well-Being Among Virally Suppressed HIV-Infected Adults With CD4>500

Harsha Thirumurthy[1]; Aleksandra Jakubowski[1]; James G. Kahn[2]; Norton Sang[5]; Tamara Clark[2]; Edwin Charlebois[2]; Maya Petersen[3]; Moses R. Kamya[4]; Diane Havlir[2]
SEARCH Collaboration

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, US; [2]University of California San Francisco, San Francisco, CA, US; [3]University of California Berkeley School of Public Health, Berkeley, CA, US; [4]Makerere University College of Health Sciences, Kampala, Uganda; [5]KEMRI, Kisumu, Kenya

Session P-W7 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HIV Stigma

1057 Internalized Stigma in a Population-Based Sample of US HIV-Infected Adults in Care

Amy R. Baugher; Linda Beer; Jennifer L. Fagan; Christine L. Mattson; Mark Freedman; Jacek Skarbinski

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

1058 Association Between Enacted Stigma and HIV-Related Risk Behavior Among MSM, National HIV Behavioral Surveillance System, 2011

Alexandra B. Balaji; Justin C. Smith; Kristina Bowles; Gabriela Paz-Bailey

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

1059 Has Antiretroviral Treatment Scale-Up in Sub-Saharan Africa Reduced HIV-Related Stigma in the General Population? A Cross-Country Analysis

Brian T. Chan[1]; Alexander Tsai[2]; Mark Siedner[2]

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

Session P-W8 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Serosorting and Seroadaptive Behavior: What's Your Position?

1060 Trends in Sexual Behaviors Among Men Who Have Sex With Men in the United States, the Role of Antiretroviral Therapy and Seroadaptive Strategies

Gabriela Paz-Bailey[1]; Maria Mendoza[1]; Binh Le[1]; Charles E. Rose[1]; Teresa Finlayson[1]; Cyprian Wejnert[1]; Henry F. Raymond[2]; Joseph Prejean[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]San Francisco Department of Public Health, San Francisco, CA, US

1061 Changes in Condomless Sex and Serosorting Among MSM After HIV Diagnosis

Christine M. Khosropour[2]; Julia C. Dombrowski[2]; David A. Katz[2]; Matthew R. Golden[2]

[1]University of Washington, Seattle, WA, US; [2]University of Washington, Seattle, WA, US

1062 Serosorting and Sexual Risk Behavior Influenced by Perceived HIV Serostatus Among MSM

Kathleen A. Brady; Jennifer Shinefeld; Catherine Mezzacappa

Philadelphia Department of Public Health, Philadelphia, PA, US

1063 Use of the Seroadaptive Strategies of Sexual Positioning and Serosorting by MSM in Nigeria

Cristina M. Rodriguez-Hart[1]; Hongjie Liu[2]; Ifeanyi K. Orazulike[3]; Sam Zorowitz[4]; Sylvia Adebajo[5]; Lindsay Hughes[6]; Stefan Baral[7]; Merlin L. Robb[6]; William Blattner[1]; Manhattan Charurat[1]

[1]University of Maryland School of Medicine, Baltimore, MD, US; [2]University of Maryland School of Public Health, College Park, MD, US; [3]International Center on Advocacy and Rights to Health, Abuja, Nigeria; [4]Massachusetts General Hospital and Harvard Medical School, Boston, MA, US; [5]Population Council, Abuja, Nigeria; [6]US Military HIV Research Program, Bethesda, MD, US; [7]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

TUESDAY, FEBRUARY 24, 2015

Session P-X1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Paying for Care

1064 Ryan White HIV/AIDS Program Assistance and HIV Treatment Outcomes in the United States

Heather Bradley[1]; Abigail H. Viall[1]; Pascale M. Wortley[1]; Antigone Dempsey[2]; Heather Hauck[2]; Jacek Skarbinski[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]US Health Resources and Services Administration, Rockville, MD, US

1065 Combining Multisite Payor Data With Clinical Data to Quantify Medicaid Payments for HIV Care

Anne Monroe[1]; Cindy Voss[1]; Richard Moore[1]; Kelly Gebo[1]; Allison Agwu[1]; Richard Rutstein[3]; Victoria Sharp[5]; Stephen Boswell[4]; John Fleishman[2]
The HIV Research Network

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Agency for Healthcare Research and Quality, Rockville, MD, US; [3]The Children's Hospital of Philadephia, Philadelphia, PA, US; [4]Fenway Health, Boston, MA, US; [5]Wyckoff Heights Medical Center, Brooklyn, NY, US

1066 Proportionately More Gay Men in Seattle Insured Following the Affordable Care Act

Julia E. Hood[1]; Susan E. Buskin[1]; Elizabeth A. Barash[1]; Julia C. Dombrowski[2]; Matthew R. Golden[2]

[1]Public Health–Seattle & King County, Seattle, WA, US; [2]University of Washington, Seattle, WA, US

1067 Characteristics and Outcomes of Patients Seeking Care at a New "Co-Pay" Convenience Clinic Established to Explore Sustainable Funding Models in Uganda

Rosalind M. Parkes-Ratanshi[1]; Gerald Mukisa[1]; Tom Kakaire[1]; Faridah Mayanja[1]; Adelline Tumikye[1]; Brenda Mitchell[1]; Shadia Nakalema[1]; Walter Schlech[2]

[1]Makerere University College of Health Sciences, Kampala, Uganda; [2]Dalhousie University, Halifax, Canada

WEDNESDAY, FEBRUARY 25, 2015

Session P-X2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Linkage to and Retention in Care

1068 A Longitudinal Approach to Retention and Virologic Suppression Across the HIV Care Continuum

Jonathan Colasanti; Carlos del Rio; Wendy Armstrong

Emory University School of Medicine, Atlanta, GA, US

1069 A High Proportion of Persons Diagnosed With Acute HIV Achieve Viral Suppression

Emily Westheimer[1]; Philip J. Peters[2]; Rebekkah Robbins[3]; Sarah L. Braunstein[3]

[1]New York City Department of Health and Mental Hygiene, Queens, NY, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [3]New York City Department of Health and Mental Hygiene, Queens, NY, US

1070 Drivers of HIV Treatment Success Among a Population-Based Sample of Younger Black MSM

John A. Schneider[1]; Britt Skaathun[1]; Stuart Michaels[2]; Lindsay Young[1]; Keith Green[1]; Ethan Morgan[1]; Robert W. Coombs[3]; Sam Friedman[4]; Edward Laumann[1]
On behalf of UConnect Study Team

[1]University of Chicago, Chicago, IL, US; [2]NORC, Chicago, IL, US; [3]University of Washington, Seattle, WA, US; [4]National Development Research Institute, New York, NY, US

1071 Population-Level HIV RNA and CD4+ Distribution in a Rural Ugandan Community With Widespread Community HIV Testing and Universal ART Access

Vivek Jain[1]; Gabriel Chamie[1]; Gideon Amanyire[2]; Dalsone Kwarisiima[2]; Jane Kabami[2]; Maya L. Petersen[3]; Tamara Clark[1]; Edwin D. Charlebois[1]; Moses R. Kamya[2]; Diane Havlir[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Makerere University–University of California San Francisco Research Collaboration, Kampala, Uganda; [3]University of California Berkeley School of Public Health, Berkeley, CA, US

1072 Facility-Level Factors Influencing Retention in HIV Care in East Africa

Beth Rachlis[1]; Giorgos Bakoyannis[2]; Philippa Easterbrook[3]; R. Scott Braithwaite[4]; Craig R. Cohen[5]; Elizabeth Bukusi[6]; Andrew D. Kambugu[3]; Mwebesa Bosco Bwana[7]; Elvin H. Geng[5]; Paula Braitstein[1]

[1]Academic Model Providing Access to Healthcare program, Eldoret, Kenya; [2]Indiana University, School of Medicine, Indianapolis, IN, US; [3]Infectious Diseases Institute, Kampala, Uganda; [4]New York University, New York City, NY, US; [5]University of California San Francisco (UCSF), San Francisco, CA, US; [6]Kenya Medical Research Institute, Nairobi, Kenya; [7]Mbarara University, Mbarara, Uganda

1073 Patient Retention in HIV Care Is Related to Point of Diagnosis in Western Kenya

Becky L. Genberg[1]; Hana Lee[1]; Fatma Some[2]; Joseph Hogan[1]; Paula Braitstein[3]

[1]Brown University, Providence, RI, US; [2]Moi University School of Medicine, Eldoret, Kenya; [3]Indiana University, School of Medicine, Indianapolis, IN, US

1074 Successful Down-Referral Even Among Patients With Virologic Failure in South Africa

Jonathan Colasanti[1]; Darius McDaniel[2]; Brent Johnson[2]; Henry Sunpath[4]; Carlos del Rio[1]; Vincent C. Marconi[1]

[1]Emory University School of Medicine, Atlanta, GA, US; [2]Emory University Rollins School of Public Health, Atlanta, GA, US; [3]Emory University Rollins School of Public Health, Atlanta, GA, US; [4]McCord Hospital, Durban, South Africa

1075 Retention in a Decentralized HIV Care and Treatment Program in North Central Nigeria

Patricia Agaba[1]; Becky L. Genberg[2]; Solomon Sagay[1]; Oche Agbaji[1]; Nancin Dadem[3]; Grace Kolawole[3]; Prosper Okonkwo[3]; Seema Meloni[4]; Phyllis Kanki[4]; Norma C. Ware[5]

[1]University of Jos, Jos, Nigeria; [2]Brown University, Providence, RI, US; [3]AIDS Prevention Initiative, Abuja, Nigeria; [4]Harvard School of Public Health, Boston, MA, US; [5]Harvard Medical School, Boston, MA, US

1076 Patient Level Findings: Pre-ART Mortality and Its Determinants in Tanzania Public-Driven HIV Care Program (2004-2011)

Bonita K. Kilama[1]; Candida Moshiro[2]; Jim Todd[4]; Angela Ramadhani[1]; Donan Mmbando[3]

[1]National AIDS Control Program, Dar es Salaam, United Republic of Tanzania; [2]Muhimbili University of Health and Allied Sciences, Dar es Salaam, United Republic of Tanzania; [3]Ministry of Health Of Social Welfare, Dar es Salaam, United Republic of Tanzania; [4]London School of Hygiene and Tropical Medicine, London, United Kingdom

1077 Impact of the Ebola Outbreak on the Quality of Care of People Living With HIV Taking Antiretroviral Treatment at Donka National Hospital in Conakry, Guinea

Mohamed Cisse[2]; Mohamadou Saliou Diallo[4]; Cheick Tidiane Tidiane[3]; Cece Kpamou[4]; Justeau Dimitri[4]; Eric Dortenzio[1]; **Jacques D. Ndawinz**[1]

[1]Solthis International NGO, Paris, France; [2]Hôpital National de Donka, Conakry, Guinea; [3]Ministre de la Santé et de l'Hygiène Publique, Conakry, Guinea; [4]Solthis NGO, Conakry, Guinea

1078 The African Diaspora Health Initiative: Enhancing Access to Health Care for African and Caribbean Immigrant Populations in Philadelphia

Helena Kwakwa; Rahab Wahome; Oumar H. Gaye; Natasha Z. Mvula

Philadelphia Department of Public Health, Philadelphia, PA, US

THURSDAY, FEBRUARY 26, 2015

Session P-X3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Guidelines and Their Implementation

1079 Starting ART at 500 CD4 in Southern Africa: What Is the Impact on ART Eligibility?

Helena Huerga[1]; David Maman[1]; Gilles Van Cutsem[2]; Beatrice Kirubi[3]; Charles Masiku[4]; Ruggero G. Giuliani[2]; Irene Mukui[5]; Benson Chilima[6]; Elisabeth Szumilin[7]; Jean-François Etard[1]

[1]Epicentre, Paris, France; [2]Médecins Sans Frontières, Cape Town, South Africa; [3]Médecins Sans Frontières, Nairobi, Kenya; [4]Médecins Sans Frontières, Lilongwe, Malawi; [5]National AIDS and STDs Control Program, Nairobi, Kenya; [6]Ministry of Health, Lilongwe, Malawi; [7]Médecins Sans Frontières, Paris, France

1080 Impact of South Africa's HIV Treatment Guidelines on Early Losses: A Cohort Analysis

Ingrid T. Katz[1]; Richard Kaplan[2]; Garrett Fitzmaurice[4]; Dominick Leone[3]; David R. Bangsberg[1]; Linda-Gail Bekker[2]; Catherine Orrell[2]

[1]Harvard Medical School, Cambridge, MA, US; [2]Desmond Tutu HIV Foundation, Cape Town, South Africa; [3]Boston University School of Medicine, Boston, MA, US; [4]Harvard School of Public Health, Boston, MA, US

1081 Mortality Across Two ART Trials Enrolling at ≤200 vs ≤350 CD4 cells/uL in Kenya

Rachel A. Silverman[1]; Michael Chung[1]; James N. Kiarie[2]; Nelly Yatich[1]; Julia Njoroge[1]; Catherine Kiptiness[1]; Samah Sakr[3]; Grace John-Stewart[1]; Lisa Frenkel[1]

[1]University of Washington, Seattle, WA, US; [2]University of Nairobi, Nairobi, Kenya; [3]Coptic Hospital, Nairobi, Kenya

1082 HIV Testing of Persons Aged 15–65 Years at Visits to US Physician Offices, 2009–2010

Karen Hoover; Shirley Lecher; Roman Gvetadze; Philip Peters

US Centers for Disease Control and Prevention, Atlanta, GA, US

1083 Frontline Practices With HIV Prevention: A Survey of US Infectious Disease Physicians

Douglas S. Krakower[1]; Susan E. Beekmann[2]; Philip M. Polgreen[2]; Kenneth H. Mayer[1] Emerging Infections Network

[1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US; [2]University of Iowa, Iowa City, IA, US

Session P-Y1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Male Circumcision: Risk, Innovation, and Scale-Up

1084 HSV-2 Shedding From Male Circumcision Wounds Among HIV-Infected Men

Mary K. Grabowski[1]; Godfrey Kigozi[2]; Ronald H. Gray[1]; Jordyn L. Manucci[3]; David Serwadda[4]; Eshan U. Patel[3]; Fred Nalugoda[2]; Maria J. Wawer[1]; Thomas C. Quinn[5]; Aaron A. Tobian[3]

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]Rakai Health Sciences Program, Kalisizo, Uganda; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]Makerere University College of Health Sciences, Kampala, Uganda; [5]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

1085 Association Between Foreskin Microbiota and Local Cytokines in Men From Rakai, Uganda

Cindy M. Liu[1]; Aaron A. Tobian[1]; Jessica Prodger[2]; David Serwadda[3]; Godfrey Kigozi[3]; Fred Nalugoda[3]; Maria J. Wawer[2]; Lance Price[4]; Rupert Kaul[5]; Ronald H. Gray[2]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]Rakai Health Sciences Program, Rakai, Uganda; [4]Translational Genomics Research Institute, Flagstaff, AZ, US; [5]University of Toronto, Toronto, Canada

1086 Mobile VMMC Teams in Tanzania See Older Clients and Have Higher Followup Rates

Augustino M. Hellar[1]; Dorica Boyee[1]; Hally Mahler[1]; Marya Plotkin[1]; Touma Ng'wanakilala[1]; Kelly Curran[2]; Tigistu Ashengo[2]; Hawa Mziray[1]; Erick Mlanga[3]; Sifuni Koshuma[4]

[1]Jhpiego, Dar es Salaam, United Republic of Tanzania; [2]Jhpiego, Baltimore, MD, US; [3]US Agency for International Development, Dar es Salaam, United Republic of Tanzania; [4]Ministry of Health and Social Welfare, Iringa, United Republic of Tanzania

1087 High Acceptability of PrePex™ Device in Routine Programmatic Settings in Rwanda

Eugene Rugwizangoga[1]; Beata Mukarugwiro[1]; Jovite Sinzahera[1]; Alphonse Mutabaruka[1]; Gloriose Abayisenga[1]; J.D. Ntakakirabose[1]; Ngeruka Leon[4]; Eugene Zimulinda[3]; Kelly Curran[2]; Tigistu Ashengo[2]

[1]Jhpiego/Rwanda, Kigali, Rwanda; [2]Jhpiego, an Affiliate of Johns Hopkins University, Washington, DC, US; [3]US Department of Defense, Rwanda, Kigali, Rwanda; [4]Rwanda Military Hospital, Kigali, Rwanda

1088 Self-Selection of Circumcision Acceptors, Risk Compensation and Effectiveness of Circumcision Among Service Recipients, Rakai, Uganda

Joseph Kagaayi[1]; Xiangrong Kong[2]; Godfrey Kigozi[1]; Fred Nalugoda[1]; Steven J. Reynolds[3]; David Serwadda[4]; Nelson K. Sewankambo[5]; Maria J. Wawer[2]; Ronald H. Gray[2]

[1]Rakai Health Sciences Program, Entebbe, Uganda; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, US; [4]Makerere University School of Public Health, Kampala, Uganda; [5]Makerere University College of Health Sciences, Kampala, Uganda

1089 Potential Protection From HIV Transmission by Penile Cuttings in Papua New Guinea

Ivy H. Shih[1]; Lester Asugeni[2]; Matthew David[5]; Paul Horwood[5]; Parana Hewage Mangalasir[3]; David Mc Laren[3]; Rachael Tommbe[2]; Andrew Vallely[1]; Arnold Waine[4]; Stuart G. Turville[1]

[1]The Kirby Institute, Sydney, Australia; [2]Pacific Adventist University, Port Moresby, Papua New Guinea; [3]James Cook University, Cairns, Australia; [4]University of Papua New Guinea, Port Moresby, Papua New Guinea; [5]Papua New Guinea Institute of Medical Health, Goroka, Papua New Guinea

WEDNESDAY, FEBRUARY 25, 2015

Session P-Y2 Poster Session — Poster Hall
2:30 pm – 4:00 pm

Linkage to Care and ART Initiation

1090 Linkage to HIV Care Following Home-Based Testing and CD4 in Rural Malawi

Sophie Masson[1]; Jihane Ben Farhat[1]; Charles Masiku[4]; Benson Chilima[2]; Elisabeth Szumilin[3]; Leon Salumu[3]; Jean-François Etard[1]; **David Maman**[1]

[1]Epicentre/Médecins Sans Frontières, Paris, France; [2]Ministry of Health, Lilongwe, Malawi; [3]Médecins Sans Frontières, Paris, France; [4]Médecins Sans Frontières Malawi, Lilongwe, Malawi

1091 Rapid ART Initiation Reduces Loss Between HIV Testing and Treatment: The RapIT Trial

Sydney Rosen[1]; Mhairi Maskew[2]; Matt P. Fox[1]; Cynthia Nyoni[2]; Constance Mongwenyana[2]; Given Malete[2]; Ian Sanne[2]; Julia K. Rohr[1]; Lawrence Long[2]

[1]Boston University, Boston, MA, US; [2]University of the Witwatersrand, Johannesburg, South Africa

1092 Outcomes of a Clinic-Health Department "Data to Care" Relinkage Intervention

Joanna M. Bove[2]; Matthew R. Golden[2]; Shireesha Dhanireddy[2]; Robert Harrington[2]; Julie Dombrowski[2]

[1]University of Washington, Seattle, WA, US; [2]University of Washington, Seattle, WA, US

1093 HIV Partner Services Can Achieve Near-Universal Linkage to HIV Care

David A. Katz[1]; Julia C. Dombrowski[1]; Susan E. Buskin[2]; Amy Bennett[2]; Elizabeth A. Barash[2]; Matthew R. Golden[1]

[1]University of Washington, Seattle, WA, US; [2]Public Health - Seattle & King County, Seattle, WA, US

1094 Immunodeficiency at the Start of ART: A Global View

Klea Panayidou[1]; Ole Kirk[3]

On behalf of the IeDEA Collaboration and the COHERE Collaboration

[1]University of Bern, Bern, Switzerland; [2]Université Victor Segalen Bordeaux 2, Bordeaux cedex, France; [3]University of Copenhagen, Copenhagen, Denmark

1095 Providers' Attitudes and Practices Related to ART Use for HIV Care and Prevention

Kate Buchacz[1]; Jennifer Farrior[2]; Gheetha Beauchamp[3]; Laura McKinstry[3]; Ann Kurth[4]; Barry S. Zingman[5]; Fred Gordin[6]; Deborah Donnell[3]; Wafaa M. El-Sadr[7]; Bernard M. Branson[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]FHI360, Durham, NC, US; [3]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [4]New York University School of Medicine, New York, NY, US; [5]Montefiore Medical Center and Albert Einstein College of Medicine, New York, NY, US; [6]Veterans Affairs Medical Center and George Washington University, Washington, DC, US; [7]Columbia University and Harlem Hospital, New York, NY, US

Session P-Y3 Poster Session — Poster Hall
2:30 pm – 4:00 pm

HIV Testing: Innovations and Scale-Up

1096 Availability and Quality of Online HIV Self-Test Kits in China and the United States

Fengying Liu[2]; Larry Han[3]; **Weiming Tang**[1]; Shujie Huang[2]; Ligang Yang[2]; Heping Zheng[2]; Bin Yang[2]; Joseph Tucker[1]

[1]University of North Carolina, Guangzhou, China; [2]Guangdong Provincial STD Control Center, Guangzhou, China; [3]University of North Carolina, Chapel Hill, NC, US

1097 Home HIV Testing and Medical Care: Doing the Right Thing

Charulata J. Sabharwal; Sharmila Shah; Chi-Chi N. Udeagu

New York City Department of Health and Mental Hygiene, Queens, NY, US

1098 Using Grindr™, a Social-Media–Based Application, to Increase HIV Self Testing Among High-Risk Men Who Have Sex With Men in Los Angeles, California, 2014

Alexandra Medline[1]; Emily Huang[2]; Robert Marlin[2]; Sean D Young[2]; Justin Kwok[2]; Jeffrey D. Klausner[2]

[1]McGill University, Toronto, Canada; [2]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US

1099 Sexually Transmitted Disease Partner Services Increase HIV Testing Among Men Who Have Sex With Men

Matthew R. Golden[1]; David A. Katz[1]; David Kern[2]; David Heal[2]; Roxanne Kerani[1]; Julia C. Dombrowski[1]

[1]University of Washington, Seattle, WA, US; [2]Washington State Department of Health, Tumwater, WA, US

1100 Expanding HIV Testing in Hospital Emergency Departments and Inpatient Admissions

Pollyanna R. Chavez[1]; Elizabeth Greene[2]; Kate Buchacz[1]; Theresa Gamble[2]; Steven F. Ethridge[1]; Laura McKinstry[3]; Gheetha Beauchamp[3]; Matthew Connor[3]; Wafaa M. El-Sadr[4]; Bernard M. Branson[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]FHI360, Durham, NC, US; [3]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [4]Columbia University, New York, NY, US

1101 Universal HIV Testing Using a "Hybrid" Approach in East Africa in the SEARCH Trial

Gabriel Chamie[1]; Tamara Clark[1]; Jane Kabami[3]; Kevin Kadede[2]; Dalsone Kwarisiima[3]; Norton Sang[2]; Maya Petersen[4]; Moses R. Kamya[3]; Diane Havlir[1]; Edwin Charlebois[5]

[1]University of California San Francisco, San Francisco, CA, US; [2]Kenyan Medical Research Institute (KEMRI), Nairobi, Kenya; [3]Makerere University - University of California Research Collaboration, Kampala, Uganda; [4]University of California Berkeley School of Public Health, Berkeley, CA, US; [5]University of California San Francisco (UCSF), San Francisco, CA, US

1102 A Household Food Voucher Increases Consent to Home-Based HIV Testing in Rural KwaZulu-Natal

Mark McGovern[1]; David Canning[1]; Frank Tanser[2]; Kobus Herbst[2]; Dickman Gareta[2]; Tinofa Mutevedzi[2]; Deenan Pillay[2]; Till Barnighausen[1]

[1]Harvard University, Cambridge, MA, US; [2]Wellcome Trust Africa Centre for Health and Population Studies, University of KwaZulu-Natal, KwaZulu-Natal, South Africa

1103 Acceptability and Uptake of Home-Based HIV Self-Testing in Lesotho

Allison V. Zerbe[1]; Abby L. DiCarlo[1]; Joanne E. Mantell[2]; Robert H. Remien[2]; Danielle D. Morris[1]; Koen Frederix[1]; Blanche Pitt[1]; Zachary J. Peters[1]; Wafaa M. El-Sadr[1]

[1]ICAP at Columbia University, New York, NY, US; [2]HIV Center for Clinical and Behavioral Studies, New York State Psychiatric Institute & Columbia University, New York, NY, US

TUESDAY, FEBRUARY 24, 2015

Session P-Z1 Poster Session — Poster Hall
2:30 pm – 4:00 pm

Costs and Cost Effectiveness

1104 The Lifetime Medical Cost Savings From Preventing HIV in the United States

Bruce R. Schackman[1]; John Fleishman[6]; Amanda Su[2]; Richard Moore[5]; Rochelle Walensky[2]; David Paltiel[3]; Milton Weinstein[4]; Kenneth Freedberg[2]; Kelly Gebo[5]; Elena Losina[2]

[1]Weill Cornell Medical College, New York, NY, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Yale School of Public Health, New Haven, CT, US; [4]Harvard School of Public Health, Boston, MA, US; [5]Johns Hopkins University School of Medicine, Baltimore, MD, US; [6]Agency for Healthcare Research and Quality, Rockville, MD, US

1105 Online Partner Notification: A Cost-Effective Tool to Reduce HIV-1 Epidemic Among MSM

Brooke E. Nichols[1]; Hannelore M. Götz[2]; Eric C. van Gorp[1]; Annelies Verbon[3]; Casper Rokx[3]; Charles Boucher[1]; David A. van de Vijver[1]

[1]Erasmus University Medical Center, Rotterdam, Netherlands; [2]Public Health Service Rotterdam-Rijnmond, Rotterdam, Netherlands; [3]Erasmus Medical Center, Rotterdam, Netherlands

1106 Cost-Effectiveness of Preexposure Prophylaxis for High-Risk HIV-Discordant Couples

Roger Ying[1]; Renee Heffron[1]; Jared Baeten[1]; Connie Celum[1]; Elly Katabira[2]; Nulu Bulya[2]; Ruanne V. Barnabas[1]

[1]University of Washington, Bellevue, WA, US; [2]Makerere University College of Health Sciences, Kampala, Uganda

1107 Multipurpose Prevention Technologies for HIV and Pregnancy Prevention

Rebecca Geary; **Jennifer Smith**; Nidhi Khurana; Ide Cremin; Timothy Hallett

Imperial College London, London, United Kingdom

1108 Cost-Effectiveness of Isoniazid Preventative Therapy for HIV-Infected Pregnant Women in India

Sunaina Kapoor; Natasha Chida; Amita Gupta; **Maunank Shah**

Johns Hopkins University School of Medicine, Baltimore, MD, US

1109 Epidemiologic Benefits and Cost-Effectiveness of Improving Rwanda's HIV Care Cascade

Eran Bendavid[1]; Edward Mills[2]; Steve Kanters[2]; Sabin Nsanzimana[3]

[1]Stanford University, Stanford, CA, US; [2]University of Ottawa, Ottawa, Canada; [3]Rwanda Biomedical Center, Kigali, Rwanda

1110 The Cost-Effectiveness of Early ART Initiation in South Africa: A Quasi-Experiment

Jacob Bor[1]; Ellen Moscoe[2]; Natsayi Chimbindi[3]; Kobus Herbst[3]; Kevindra K. Naidu[3]; Frank Tanser[3]; Deenan Pillay[3]; Till Barnighausen[3]

[1]Boston University School of Public Health, Boston, MA, US; [2]Harvard School of Public Health, Boston, MA, US; [3]Wellcome Trust Africa Centre for Health and Population Studies, Somkhele, South Africa

1111 Community-Based Strategies to Strengthen the Continuum of HIV Care Are Cost-Effective

Jennifer A. Smith[1]; Monisha Sharma[2]; Carol Levin[2]; Jared Baeten[2]; Heidi van Rooyen[3]; Connie Celum[2]; Timothy Hallett[1]; Ruanne V. Barnabas[2]

[1]Imperial College London, London, United Kingdom; [2]University of Washington, Seattle, WA, US; [3]Human Sciences Research Council, Sweetwaters, South Africa

1112 The Cost-Effectiveness of CD4 Cell Count Versus HIV RNA Viral Load for ART Initiation

Roger Ying[1]; Brian Williams[3]; Ruanne V. Barnabas[1]; Reuben Granich[2]

[1]University of Washington, Bellevue, WA, US; [2]Joint United Nations Programme on HIV/AIDS, Geneva, Switzerland; [3]Stellenbosch University, Stellenbosch, South Africa

1113 Costs of Expanded HIV Testing in 4 EDs: Results From HPTN 065

Bruce R. Schackman[1]; Ashley A. Eggman[1]; Jared A. Leff[1]; Megan Braunlin[1]; Bernard M. Branson[2]

[1]Weill Cornell Medical College, New York, NY, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

1114 Global Fund Cost Projections for Implementing WHO 2013 Guidelines

Obinna Onyekwena; Ade Fakoya; Michael Johnson; Michael Olszak-Olszewski; Mark Dybul

The Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland

WEDNESDAY, FEBRUARY 25, 2015

Session P-Z2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Modeling HIV Epidemiology

1115 Estimating the Number and Characteristics of Male-Male HIV Transmissions in the USA

Eli S. Rosenberg[1]; Jeremy Grey[1]; Gabriela Paz-Bailey[2]; H. Irene Hall[2]; Amy Lansky[2]; Jonathan Mermin[2]; Jacek Skarbinski[2]

[1]Emory University Rollins School of Public Health, Atlanta, GA, US; [2]Centers for Disease Control and Prevention, Atlanta, GA, US; [3]CDC, Atlanta, GA, US

1116 Acute HIV Infection Transmission Among People Who Inject Drugs in an Established Epidemic Setting

Daniel Escudero[4]; Caleb Weinreb[4]; Mark Lurie[4]; Kenneth Mayer[2]; Sandro Galea[3]; Samuel Friedman[5]; Brandon Marshall[4]

[1]Brown University, Providence, RI, US; [2]Fenway Health, Boston, MA, US; [3]Columbia University, New York, NY, US; [4]Brown University, Providence, RI, US; [5]National Development and Research Institutes, Inc, New York, NY, US

1117 Decreasing Number of Undiagnosed HIV Infections in the Netherlands

Ard van Sighem[1]; Fumiyo Nakagawa[3]; Daniela De Angelis[4]; Chantal Quinten[5]; Daniela Bezemer[1]; Eline Op de Coul[2]; Matthias Egger[7]; Frank de Wolf[6]; Christophe Fraser[6]; Andrew N. Phillips[3]

[1]Stichting HIV Monitoring, Amsterdam, Netherlands; [2]National Institute for Public Health and the Environment, Bilthoven, Netherlands; [3]University College London, London, United Kingdom; [4]MRC Biostatistics Unit, Cambridge, United Kingdom; [5]Europen Centre for Disease Prevention and Control, Stockholm, Sweden; [6]Imperial College London, London, United Kingdom; [7]Institute for Social and Preventive Medicine, University of Bern, Bern, Switzerland

THURSDAY, FEBRUARY 26, 2015

Session P-Z3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Modeling the Impact of HIV Interventions

1118 Predicted Impact of Antiretroviral Treatment on Preventing New HIV Infections in 53 Low- and Middle-Income Countries With Large HIV Epidemics

Andrew M. Hill[1]; Anton Pozniak[1]; Katherine Heath[2]; Alice Raymond[2]; Mary Mahy[3]; Nathan Ford[4]

[1]Chelsea and Westminster Hospital, London, United Kingdom; [2]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom; [3]Joint United Nations Programme on HIV/AIDS (UNAIDS), Geneva, Switzerland; [4]World Health Organization, Geneva, Switzerland

1119 Survival Benefits Attributable to the Brazilian National ART Policy

Paula M. Luz[1]; Michael P. Girouard[2]; Beatriz Grinsztejn[1]; Kenneth Freedberg[2]; Valdilea Veloso[1]; Elena Losina[4]; Claudio Struchiner[1]; Robert Parker[2]; David Paltiel[3]; Rochelle Walensky[2]

[1]Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil; [2]Massachusetts General Hospital, Boston, MA, US; [3]Yale School of Public Health, New Haven, CT, US; [4]Brigham and Women's Hospital, Boston, MA, US

1120 A Predictive Risk Model for First-Line Treatment Failure in South Africa

Julia K. Rohr[1]; Prudence Ive[2]; Rebecca H. Berhanu[2]; Kate Shearer[2]; Mhairi Maskew[2]; Lawrence Long[2]; Ian Sanne[2]; Matthew P. Fox[1]

[1]Boston University School of Public Health, Boston, MA, US; [2]University of Witwatersrand, Johannesburg, South Africa; [3]Right to Care, Johannesburg, South Africa

1121 U.S. Population Benefits of HIV Preexposure Prophylaxis for Injection Drug Users

Cora Bernard[1]; Margaret L. Brandeau[1]; Douglas K. Owens[2]; Keith Humphreys[2]; Eran Bendavid[1]; Mark Holodniy[2]; Christopher Weyant[1]; Jeremy D. Goldhaber-Fiebert[1]

[1]Stanford University, Stanford, CA, US; [2]VA Palo Alto Health Care System, Palo Alto, CA, US

1122 Procreation in HIV-Serodiscordant Couples: TasP, PrEP, or Assisted Reproduction?

Guillaume Mabileau[1]; Michaël Schwarzinger[1]; Juan Flores[1]; Catherine Patrat[2]; Dominique Luton[2]; Sylvie Epelboin[2]; Laurent Mandelbrot[3]; Sophie Matheron[2]; Yazdan Yazdanpanah[2]
On behalf of ANRS 12008

[1]Inserm, Paris, France; [2]AP-HP, Bichat-Claude Bernard Hospital, Paris, France; [3]Louis Mourier Hospital, Colombes, France

ORAL ABSTRACTS

MONDAY, FEBRUARY 23, 2015

Session W1 Workshop **Room 6E**
9:00 am – 12:30 pm

Program Committee Workshop for New Investigators and Trainees

1 A Path to an HIV Vaccine

Galit Alter
Ragon Institute of MIT, MGH and Harvard, Cambridge, MA, US

Background: Despite our growing antiviral armamentarium and our clear appreciation on how HIV infection may be blocked, HIV continues to spread like wildfire in some communities globally. Thus a vaccine is desperately needed. The HIV vaccine community has experienced renewed optimism over the past decade due to: 1) our growing appreciation for novel unexpected immune correlates of infection in the RV144 vaccine trial that showed moderate protection from infection, as well as 2) our growing capacity to identify and mechanistically profile novel neutralizing antibodies with remarkable antiviral potency. However, despite these advances, to date, it is still incompletely understood how such responses can be induced via vaccination, or how they emerge naturally during infection.

Conclusion: This presentation will therefore highlight our current understanding of the immunological profile of "protective" anti-HIV immunity, will review the "rational" vaccine design strategies that are being exploited in the vaccine field, as well as dissect the unexplored and untapped research opporutinities in the field. Throughout the presentation, information will be provided on where and when the latest information will be presented at CROI.

2 Animal Models of HIV Prevention and Cure

Guido Silvestri
Emory University, Decatur, GA, US

While the availability of very potent anti-retroviral therapy (ART) regimens has dramatically reduced the mortality and morbidity associated with HIV infection, the absence of a safe and effective AIDS vaccine and the inability to eradicate or functionally "cure" the infection remain major challenges in contemporary HIV/AIDS research. In this context, basic and translational research in the areas of HIV pathogenesis, prevention, and therapy has long benefited from the availability of animal models that allow the in vivo testing of novel conceptual hypothesis and intervention strategies that would be virtually impossible to test in humans.

The key animal models for HIV infection are non-human primates (NHP) such as Asian macaques, that have been extensively used in studies of candidate AIDS vaccines, and natural SIV hosts, such as sooty mangabeys and African green monkeys, that have been extensively used for comparative studies of AIDS pathogenesis. More recently several types of so-called humanized mice have been developed to allow in vivo studies of the interaction between HIv and the human immune system. It must be emphasize that NHP and humanized mice represent highly synergistic models that, far from being alternative to each other, are in fact each better suited to answer specific scientific questions, and therefore should be used, ideally, as complementary aspects of comprehensive experimental strategies.

In this presentation, I will briefly review the opportunities presented by the various NHP and humanized mice models to conduct studies that will improve our understanding of AIDS virology, immunology, and pathogenesis, with specific focus on studies of HIV vaccines and eradication, including those that will be presented at CROI 2015. We hope that, ultimately, pre-clinical in vivo studies in NHPs and humanized mice will inform the design of novel prevention and therapeutic strategies for HIV infection in humans.

3 HIV Prevention 2.0: What's Next?

Susan P. Buchbinder
San Francisco Department of Public Health, San Francisco, CA, US

Background: For the first 30 years of the HIV epidemic, the 3 pillars of the prevention of sexual HIV transmission focused on HIV education, testing, and condoms. These interventions, tied to community mobilization campaigns, led to dramatic declines in HIV transmission in many communities. Substantial disparities remain in HIV incidence in vulnerable populations, particularly among men who have sex with men globally, and young women in sub-Saharan Africa. However, the last few years have demonstrated that antiretrovirals can serve as powerful prevention tools – both for blocking transmission from treated HIV infected persons and blocking acquisition for HIV-uninfected persons on pre-exposure prophylaxis (PrEP). The pillars of this second generation of HIV prevention include better HIV testing strategies; scale-up of treatment as prevention; and new PrEP agents, schedules, and delivery systems. The HIV prevention pipeline now includes many new drug formulations (including long-acting injectables and vaginal rings), some of which have reached late stage testing. Phylogenetic studies are uncovering important clues about transmission networks, and modeling studies are demonstrating reasons for ongoing disparities within vulnerable populations. We anticipate results of several pivotal trials will be available in 2015.

Conclusions: We are poised to enter the 3rd major stage of HIV prevention, combining treatment as prevention and PrEP synergistically to "turn the curve" on new HIV infections and their sequelae. Challenges in achieving high HIV prevention and treatment uptake, adherence, and retention remain; addressing these gaps is a current research priority.

4 Pathogenesis of HIV Complications

Peter W. Hunt
University of California San Francisco, San Francisco, CA, US

Background: While HIV-infected individuals with access to modern antiretroviral therapy (ART) have experienced a dramatic improvement in life expectancy, they remain at higher risk than the general population for morbidity and mortality, particularly from non-AIDS complications typically associated with aging. While lifestyle factors (e.g., smoking, illicit drug use, obesity, etc) as well as ART toxicities likely play a role, it is now well recognized that abnormal immune activation and inflammation persist in many ART-suppressed individuals, including those that restore normal CD4+ T cell counts, and that the extent of these immunologic defects strongly predicts morbidity and mortality from non-AIDS conditions. Multiple causes of the persistent inflammatory state have been proposed including HIV persistence, microbial translocation, CMV and other prevalent

co-infections. While earlier initiation of ART appears to be beneficial in reducing the inflammatory state, and some commonly used medications with anti-inflammatory properties (e.g., statins) have shown some promise in pilot studies, there is a clear need for effective interventions to reverse persistent immune activation in this setting. These issues will become increasingly important as the HIV epidemic gets older, particularly in resource-limited settings, where the vast majority of HIV-infected individuals live. Yet, the most important pathways to target with novel interventions remain unclear.

Conclusions: In the context of data being presented at CROI 2015, I will review key insights from observational studies and clinical trials that help characterize the scope of the problem of persistent immune activation in treated HIV infection. I will also highlight the importance of harnessing systems biology approaches in selecting optimal interventional targets and the need for pursuing these questions in both resource-rich and resource-limited settings.

5 HIV Cure Research

John M. Coffin

Tufts University, Boston, MA, US

Background: Although current antiretroviral therapy suppresses HIV replication and halts the otherwise inevitable progression to AIDS, it is not curative. Even after a decade or more, its interruption leads inevitably to reappearance of the virus within a few weeks. These results imply the existence of a "reservoir" of HIV-infected cells capable of producing infectious virus that can reestablish active infection when antiviral drugs are no longer present. It is important to bear in mind that the true reservoir, as so defined, is a very small fraction of the total HIV-infected cells, which are stably present in individuals on therapy, of which the large majority harbor defective and whose properties may not be represented by the majority. At present, antiretroviral drugs have to be taken for life, an unsatisfactory situation due to expense, toxicity, and risk of failure. For these reasons, a major effort is underway worldwide to develop "curative" strategies that would allow cessation of therapy without return of the virus. The proof of concept that such a therapy might be possible is given by a single example: Timothy Brown, who was HIV infected and diagnosed with acute myeloid leukemia, and received 2 allogeneic bone marrow transplants from a donor whose cells were genetically defective in CCR5, and who is still HIV-free off treatment more than 5 years later. To date this experience has not been repeated, and several recent cases of sustained suppression off therapy have ended with the return of virus months to years later, so a true cure remains a distant goal, with many active lines of research directed at a number of specific, interrelated questions. 1. What is the nature and size of the reservoir? 2. How well do in vitro models of HIV latency reflect the in vivo situation? 3. Can we develop good animal models for latency and reactivation? 3. Can we reduce the reservoir size by activating expression of latent proviruses, relying on the virus or the immune system to kill the affected cell? 4. Can we "immunize" the individual (by immune or gene therapy strategies, for example) to prevent return of the virus after cessation of therapy?

Conclusions: Despite recent advances in our understanding of hIV-1 latency as well as immunology and gene therapy, cure of HIV infection remains a distant goal. I will highlight new, exciting, and unexpected data on all of these issues and how they are advancing us toward that goal.

6 Martin Delaney Presentation: How to End the HIV Epidemic: Community Perspectives

Steven F. Wakefield

HIV Vaccine Trials Network, Seattle, WA, US

Moderator: Steven F. Wakefield, HIV Vaccine Trials Network, Fred Hutch, Seattle, WA, USA

Topics and Panel Members:

Pre-exposure Prophylaxis (PrEP): Damon L. Jacobs, LMFT, New York New York, USA

Treatment as Prevention (TasP): Connie L. Celum, MD, MPH, University of Washington, Seattle, WA, USA

Cure-Related Research: Matt Sharp, Project Inform, San Francisco, CA, USA

Background: The battle to end HIV has included the community-led safe sex movement in the 1980s, through lobbying for HIV treatments in the 1990s, to current efforts to achieve significant reductions in HIV transmission and cure research. In just over thirty years we've gone from "diagnosis = death" to "diagnosis = manageable infection" and for most, the prospect of a pretty normal lifespan. Advocacy and partnerships between communities and researchers has resulted in a sense an end is achievable.

Conclusions: Each strategy to end the epidemic presents new information and opportunities for decisions about translating science into useful strategies. A licensed marriage/family therapist / advocate from explains what it means to work with people in relationships. Noting that while trying to promote a sense of empowerment, and mental and spiritual health for people infected and affected with HIV there is need for help to negotiate the boundaries and agreements and how they discuss issues around sexuality, around sexual expression. A global health MD provides insight to trials regarding epidemiology about HIV and STIs, multi-center HIV prevention trials and the role of Treatment As Prevention (TASP) in combination community-level applications. An educator and service provider diagnosed with HIV in 1988 with a long history of advocating for AIDS treatment both participates in CURE research and teaches others to become subject matter experts on priorities, ethics and concerns as the scientific community finds a way forward.

Session W2 Workshop — Room 6E

2:30 pm – 4:30 pm

Clinical Trial Design and Analysis

7 Getting SMART About Innovative Designs for Studying Effectiveness: The Case of Adaptive Implementation Interventions

Daniel Almirall

University of Michigan, Ann Arbor, MI, US

The effective treatment and management of a wide variety of health disorders, including HIV/AIDS, often requires individualized, sequential decision-making. To do this, each patient's treatment is dynamically adapted over time based on the patient's history and changing disease state. Adaptive interventions (also known as dynamic treatment regimens) operationalize individualized decision making using a sequence of decision rules that specify whether, how, for whom, or when to alter the dose, type, or delivery of pharmacological, behavioral, and/or psychosocial treatments. Recently, there has been a surge of clinical and methodological interest in developing and evaluating adaptive interventions via clinical trials. Specifically, there is great interest in the use of sequential multiple assignment randomized trials (SMART), a type of multi-stage randomized trial design, to build high-quality adaptive interventions. The primary aim of this talk is to provide a brief, conceptual introduction on adaptive interventions and SMART designs. A secondary aim is to present the design and rationale of an example SMART which aims to develop a high-quality adaptive implementation interventions to improve the uptake/adoption of an evidence-based intervention in community settings.

8 The Clinical Pharmacology of Medication Adherence

Terrence Blaschke

Stanford University, Stanford, CA, US

Recognizing that suboptimal adherence is the major cause of treatment failure and lack of effectiveness of ARVs for PrEP, scalable interventions to improve adherence are badly needed. However, there are multiple patterns of suboptimal adherence and an understanding of the definitions and taxonomy of adherence is essential in designing interventions (Vrijens et al., Br J Clin Pharmacol. 2012; 73:691-705) Many interventions have been proposed, but to date none have been scalable and sustainable (Medication Adherence Interventions, Evidence Report No. 208. AHRQ Publication No.12-E010-EF, 2012). A limitation of most studies is the absence of reliable measures of adherence before and after an intervention. Moreover, the duration of benefit in those studies showing some increase in adherence dissipates over several months. What is needed is a scalable approach to identifying suboptimal adherence, monitoring those more likely to continue or become poorly adherent due to known predisposing factors, then focusing interventions on that cohort of patients. Due to the correspondence of drug exposure to loss of efficacy or protection from infection, sparse sampling of dosing information is insufficient, and detailed dosing information itself, shared with the patient and the provider, can significantly improve adherence. Modern technology allows detailed dosing histories to be obtained unobtrusively and collected centrally at a point in time when interventions can be applied. Combined with approaches such as Managed Problem Solving (Gross et al., JAMA Intern Med. 2013; 173:300-306) and Lifetime HIV Antiretroviral Therapy Adherence Intervention: Timing Is Everything (Bangsberg and Haberer, JAMA Intern Med. 2013; 173:306-7), progress towards scaling interventions towards populations at high risk for suboptimal adherence is now within reach.

9 Epidemiological and Biostatistical Issues in Studying Rare Events in HIV

Stephen J. Gange

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

Studies of rare events have advanced scientific understanding of HIV prevention, treatment, and pathogenesis. While the definition of what is considered 'rare' is subjective, examples include individuals who: Remain free of HIV despite persistent high exposure; Acquire HIV in prevention studies & populations with low incidence; Exhibit extremes of disease progression: rapid disease progression, long-term survivors, elite suppressors; and/or Develop particular symptoms or disease conditions that might be the result of HIV infection, therapy, and/or comorbidities;

In this presentation, I will discuss how rare events impacts and motivates innovative methods in (1) study design options for observational and interventional investigations; (2) measurement, including methods for protecting against error and bias; and (3) causal and statistical inference, including the trend away from probabilistic-based inference and the rise of machine-learning techniques.

Session W3 Workshop — Room 6D

2:30 pm – 4:30 pm

Frontiers in Laboratory Science

10 Measuring Immunity 1 Cell at a Time

Mario Roederer

Vaccine Research Center, NIAID, NIH, Bethesda, MD, US

The immune system is comprised of incredibly diverse sets of cells, each programmed to carry out overlapping sets of effector functions. Quantifying any one function provides an incomplete view of the immune response, as information about what other responses are generated is absent. Quantifying multiple responses is far superior, but when carried out on a bulk level, loses information about cellular heterogeneity, gene programs, and a myriad of interactions that may occur at the single-cell level. Since individual cells are the atomic unit of immune function, the maximum information content is achievable only by measuring these functions independently and simultaneously on a cell-by-cell basis. For this reason, flow cytometry is a powerful technology to assess immune function in settings like vaccination and pathogenesis. Taking advantage of the ability of this technology to sort individual cells while preserving viability and nucleic acids, we can extend the multiplexing of gene expression measurements.

Recent advances in fluorescent probe technology now provides us with the capability to simultaneously and independently quantify more than 30 cell-associated proteins with unheralded sensitivity. Integrating this technology with single cell transcriptomics provides a unique view of cellular functions. We choose to quantify lymphocyte-centric genes, including those encoding transcription factors, signaling molecules, effector molecules, and regulatory molecules. On a single-cell basis, we can correlate protein expression with gene expression; e.g., discordant results for the same gene reveal post-transcriptional regulatory mechanisms.

We have identified gene signatures associated with vaccine-elicited T cells as well as with productively SIV-infected cells in vivo. This technology gives us an unprecedented view into the complexity and range of immunological functions expressed by vaccine or virus-specific immune cells. Using this approach, we can search for correlates of clinical outcome based on either: quantitative gene expression; and/or cell subset representation, enumerated by groups of cells sharing gene expression profiles. These analyses give us new insights into functional immune states in pathogenesis, treatment, and vaccination.

11 Studying Heterogeneity With Single Cell RNA-Sequencing

Simon Quenneville

Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Heterogeneity is a complicated problem to study. In many contexts, researchers use purified or cultured cells, treating them as a uniform population, while often a certain degree of heterogeneity is present. Treated in bulk, the large amount of individual will allow the buffering of extreme phenotypes. Heterogeneity is often suspected, but the means of exploring the phenomena were lacking. Recently, RNA-seq technology as been optimized for single-cell analysis. This allows us to look at expression levels of a large number of individual cells and genes to describe subpopulations. We have used this method to investigate specific problems in HIV infection, I will use our example to describe the huge possibilities of this technique.

We and others have observed heterogeneity: activated CD4 T cells are not all permissive to HIV infection. For example, infecting activated cells with increasing doses of HIV particles leads to a maximum level of transduction. This maximum is also variable between individuals, ranging from a few percent cells being susceptible up to more than half. Purifying infected cells followed by a comparison with uninfected cells is interesting, but the infectious process itself is altering transcription. Single cell RNA-seq allowed us to investigate the heterogeneity in CD4 T cell population coming from permissive and non-permissive donors. We have been looking for subpopulations with differential permissivity, but also for cell markers that would allow us to identify and purify the "permissive sub-population". This presentation will overview the process, flaws and limitation of this technique and describes the pipeline we are developing.

12 Integration-Site Analysis

Frederic D. Bushman

University of Pennsylvania School of Medicine, Philadelphia, PA, US

Background: The lecture will cover analysis of HIV DNA integration sites in model systems, in HIV infected patients, and in human gene therapy.

Methods: With the development of efficient methods for DNA sequence acquistion, it has become possible to study the geomic locations of populations of integrated proviruses.

Results: Early studies showed that HIV favors integration target sites within active transcription units quite strongly. This is mediated in part by tethering to the human transcriptional mediator protein LEDGF/p75. Quantification of integration site recovery can be challenging due to distortions in abudance during PCR and other steps—however tracking using the SonicAbundance method overcomes many of these limitations. These methods and a suite of custom bioinformatic tools have been applied to samples of HIV-infected patients and human subjects gene-corrected with lentiviral vectors.

Conclusions: Analysis of integration site data can involve a number of challenges—new approaches to analysis and data visualizaiton will be presented.

13 Discovery and Modeling of Genomic Regulatory Networks With Big Data

Hamid Bolouri

Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US

High throughput sequencing, large-scale data generation projects, and web-based cloud computing are changing how computational biology is performed, who performs it, and what biological insights it can deliver. Here I review the latest developments in available data, methods and software focusing on the modeling and analysis of the gene regulatory interactions in cells. Three key findings are: (A) Although sophisticated computational resources are increasingly available to bench biologists., tailored on-going education is needed to avoid the erroneous use of these resources. (B) Current models of the regulation of gene expression are far too simplistic and need updating. (C) Integrative computational analysis of large-scale datasets is becoming a fundamental component of molecular biology. I discuss current and near term opportunities and challenges related to these three points.

Session W4 Workshop — Room 613

2:30 pm – 4:30 pm

Hepatitis C Care in the Interferon-Free Era

14 Acute HCV: Is It Still Important to Diagnose and Treat?

Arthur Y. Kim

Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

With the advent of 12 week therapies for chronic HCV with high efficacy, the impetus for early identification the acute phase of infection is no longer based on enhanced treatment efficacy. Instead, the rationale for identifying infection is to provide important counseling and care aimed at enhancing personal health and preventing secondary cases. Ongoing trials will determine whether shorter and/or less intensive courses of antivirals during the acute phase of infection will result in excellent cure rates and preserve immune responses that may be important in the prevention of reinfection after viral clearance.

15 Chronic Genotype 1 Infection

Debika Bhattacharya

University of California Los Angeles CARE Center, Los Angeles, CA, US

We will discuss major management issues specific to chronic genotype 1 infection, including methods of disease staging, timing of treatment initation, regimens for treatment, and monitoring during and after treatment.

16 HCV Genotype 3: Our Next Challenge

Arthur Y. Kim

Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

While novel therapies are able to cure the vast majority of individulas with genotype 1, those with genotype 3 have less robust options. Given that it is prevalent throughout the world and is emerging in young injection drug users, advancing therapeutic options for genotype 3 is one of our next challenges. By presenting a case of a prior nonresponder to interferon-based therapies, current and future management options for genotype 3 will be highlighted.

17 HCV Cirrhotics With Early Decompensation

Marion G. Peters

University of California San Francisco, San Francisco, CA, US

HCV cirrhotics decompensate at 5-7% per year with development of varices, ascites, hepatic encephalopathy or synthetic dysfunction. All cirrhotics should be monitored for hepatocellular carcinoma (1-4% develop HCC per year). Ultrasonography is recommended every 6 months (estimated doubling time of HCC 136 days). Quadruple–phase computed tomography or MRI is used to confirm any abnormalities seen. Cirrhotics should undergo upper endoscopy to evaluate for varices. If Grade 2 or greater varices are found, primary prophylaxis with a non-selective beta blocker (propranolol or nadolol) should be initiated to decrease the heart rate by 10%. If beta blockers cannot be tolerated, then band ligation of varices is recommended. Transjugular intrahepatic portosystemic shunting (TIPS) promptly drops portal pressure.

All patients with ascites require diagnostic paracentesis to evaluate for portal hypertension and to exclude spontaneous bacterial peritonitis. Portal hypertension is suggested when serum to ascites albumin gradient is ≥1.1 mg/dL. Management of ascites includes sodium restriction (<2 g/day) and diuretics: spironolactone combined with furosemide (ratio of 40 mg furosemide: 100 mg spironolactone, increasing as needed). With progression, ascites becomes diuretic refractory and treatment usually requires large-volume paracentesis (LVP) or TIPS. For every liter of ascites removed, 50 cc of 25% salt poor albumin iv must be given. While TIPS is associated with greater transplant-free survival than LVP, it also has a much higher rate of hepatic encephalopathy.

The new all oral direct acting antiviral agents (DAA) for HCV have permanently changed the treatment landscape for patients with end stage HCV. The current AASLD/IDSA 2014 guidelines (http://www.hcvguidelines.org) recommend that patients with decompensated cirrhosis should have an experienced HCV treater and be referred for liver transplant evaluation. Recommended regimens for genotype 1 and 4 are daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) with RBV for 12 weeks in naïve patients, and 24 weeks in prior sofosbuvir failures. If RBV intolerant, daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is recommended. The regimen for Genotype

2 and 3 HCV patients with decompensated cirrhosis is daily sofosbuvir (400 mg) and weight-based RBV for up to 48 weeks. However, these patients may have lower SVR and ongoing decompensation, so careful monitoring is required.

Opening Session **4AB Auditorium**
5:00 pm – 7:00 pm

Session NL1 Lecture
Bernard Fields Lecture

18 Hepatitis C: Light at the End of the Tunnel

Charles M. Rice
The Rockefeller University, New York, NY, US

An estimated 200 million people have been infected with hepatitis C virus (HCV) with a majority unable to clear the virus. Chronic HCV infection can lead to cirrhosis, hepatocellular carcinoma, and end-stage liver disease. It is generally believed that disease results at least in part from immune mediated inflammation. Since HCV's discovery in 1989 significant progress has been made in establishing experimental systems and unraveling the details of the virus lifecycle. Examples include viral enzyme assays, infectious molecular clones, RNA replicons and finally robust cell culture systems recapitulating the entire virus lifecycle. Definition of the human factors required for HCV entry and blunting innate immune response pathways has led to the development of a mouse model that supports HCV entry, replication and virus production. Together these tools have increased our understanding of the HCV lifecycle and revealed multiple steps for therapeutic intervention. Although painstakingly slow at times, we are finally at the cusp of a revolution in HCV treatment with the advent of well tolerated, all oral, pan genotype regimens that can achieve virologic cure rates in excess of 95%. Challenges remain but we now have the tools in hand to write the final chapter of a remarkable biomedical success story.

Session NL2 Lecture
N'Galy-Mann Lecture

19 Antiretroviral Therapy: Past, Present, and Future

David A. Cooper
Kirby Institute, University of New South Wales, Sydney, Australia

Antiretroviral therapy has saved countless lives. However, we know it to be imperfect and we are always looking for ways to improve outcomes. For treatment-naïve patients, it is time either to optimise the dose of efavirenz, or replace it altogether with integrase inhibitors in combination with two nucleosides. For people requiring a second-line treatment, new studies have confirmed the current WHO standard of care but also indicated a novel approach of two new classes of drug therapy in combination, as a public health approach without the need for resistance testing. This brings us to early treatment, which is now simple, non-toxic and beneficial in reducing transmission, but about which there has been controversy in the context of insufficient resources to cover the existing number of people needing treatment.

TUESDAY, FEBRUARY 24, 2015

Session PL-1 Plenary **4AB Auditorium**
8:30 am – 9:00 am

PrEP for HIV Prevention: What We Know and What We Need to Know for Implementation

20 PrEP for HIV Prevention: What We Know and What We Still Need to Know for Implementation

Raphael J. Landovitz
University of California Los Angeles, Los Angeles, CA, US

Tenofovir-based pre-exposure prophylaxis (PrEP) prevents HIV transmission in diverse populations. Randomized controlled trials demonstrate high levels of protection against sexually transmitted HIV for men who have sex with men (MSM) and heterosexual men and women. There are less robust data supporting the use of PrEP for prevention of parenteral transmission. Enthusiasm for widespread PrEP use is dampened by concerns about safety (both near and long term), requirements for daily or near-daily dosing, potential for viral resistance, cost, and behavioral risk compensation (increases in numbers of partners and/or less frequent condom use).

Open-label "demonstration" projects are currently under way to evaluate acceptability and uptake by at-risk populations, longer-term safety, real-world adherence, the consequences of less frequent clinical evaluations, cost effectiveness, and behavioral change. Novel adherence measures will advance our understanding of patterns of PrEP dosing, coverage of sexual activity, and the optimal support mechanisms for successful PrEP use.

Transitioning demonstration project participants to clinical care and an increased interest in PrEP have posed new and difficult challenges: What type of provider should be delivering PrEP services? What are the optimal locations for PrEP initiation and follow-up? What is known about sufficient and optimal dosing regimens? What will be the adverse event profile in real-world settings? Will there be increased resistance with more widespread PrEP use? How will PrEP be financed? How can we educate providers, public health bodies, and potential consumers – particularly those most at risk – about PrEP? What are the optimal HIV testing intervals and algorithms?

The success thus far of tenofovir-based PrEP in both clinical trials and increasingly in clinical practice, other PrEP strategies are under active investigation. These include agents that are not nucleoside analogue reverse transcriptase inhibitors, topical and long-acting injectable formulations, as well as novel preparations of new and existing antivirals. Formidable questions remain as to how to operationalize, facilitate, and streamline PrEP access to populations most at-risk for HIV acquisition locally and globally.

Session PL-2 Plenary **4AB Auditorium**

9:00 am – 9:30 am

Specific HIV Integration Sites Linked to Clonal Expansion and Persistence of Cells

21 Specific HIV Integration Sites Linked to Clonal Expansion and Persistence of Cells

Stephen H. Hughes

National Cancer Institute, Frederick, MD, US

Background: The persistence of HIV-infected cells in individuals on suppressive combination antiretroviral therapy (cART) presents a major barrier for curing HIV infections.

Methods: HIV integrates its DNA into many sites in the host genome; thus integration sites can be used as markers to identify clonally expanded cells. We identified the integration sites in PBMCs and CD4+ T cells from patients and used the data to analyze the clonal expansion of infected cells. We have started to determine the sequences of viral DNAs in clonally expanded cells; these sequences are being used to study the expression of the proviruses in the expanded cells.

Results: We have identified >2500 integration sites in PBMCs and CD4+ cells of infected individuals on cART. About 40% of the integrations were in clonally expanded cells. In one patient, more than 50% of the infected cells were from a single clone; some of the expanded clones persisted for more than 10 years. There were multiple independent integrations in the same orientation as the gene in two introns of the MKL2 and BACH2 genes; many of these integrations were in clonally expanded cells. Both BACH2 and MKL2 are involved in regulating the growth of cells. DNA rearrangements involving these genes are present in human tumors. There was no evidence forintegration in one orientation, or in specific introns, in either of these genes in large libraries prepared by infecting stimulated or unstimulated PBMCs, CD34+ cells, or HeLa cells in culture. There were, in patients, multiple independent integrations in a number of other growth related genes, many of which were associated with clonal expansion of the infected cells. These data show that HIV integration at certain sites can play a critical role in the expansion and persistence of HIV infected cells. In one case, we showed that the provirus in an expanded clone was responsible for producing the majority of the virus that was present in the blood of a patient. This shows that, in this patient, immune surveillance was not sufficient to prevent clonally expanded cells from producing virions.

Conclusions: Our findings have important implications for the development and maintenance of the viral reservoir, for designing and implementing strategies to eliminate persistent HIV infection, for the use of lentiviral vectors for gene therapy in human patients, and, possibly, for the origin of some HIV-related malignancies.

Session O-1 Oral Abstracts **Room 6AB**

10:00 am – 12:15 pm

Preventing HIV and HSV-2: What Will It Take?

22LB Pragmatic Open-Label Randomised Trial of Preexposure Prophylaxis: The PROUD Study

Sheena McCormack; David Dunn
On behalf of the PROUD Study Group

MRC Clinical Trials Unit at University College London, London, United Kingdom

Background: Randomised placebo-controlled trials have clearly demonstrated that tenofovir/emtricitabine (TDF/FTC), when taken regularly as PrEP, reduces the risk of HIV infection. However, there are concerns that this benefit might be counteracted by users of PrEP engaging in riskier sexual practices, increasing their chance of exposure to HIV and other STIs. This supports the need for pragmatic open-label randomised studies which mimic real-life clinical practice.

Methods: The PROUD study enrolled MSM from 13 sexual health clinics in England between 27Nov2012 and 30Apr2014. Eligibility criteria included a negative HIV test in the previous 4 weeks and reported condomless anal intercourse in the previous 90 days. MSM were randomised 1:1 to receive open-label daily TDF/FTC either immediately (IMM) or after a deferral (DEF) period of 12 months, and followed quarterly. Based on early demonstration of efficacy, the TSC/IDMC recommended on 13Oct2014 that all MSM in the deferral period be offered PrEP. All analyses are modified ITT (excluding 3 MSM with a reactive HIV test at baseline) based on person-years (PY) to the first HIV test after 48 weeks or after 13Oct2014, whichever was earlier.

Results: 545 MSM were randomised (276 IMM, 269 DEF). At baseline, median(IQR) age was 35(30-43) and 81% were white; median(IQR) number of anal sex partners in the previous 90 days was 10(4-20); 64% reported a diagnosed STI in the previous 12 months. 20 MSM (5 IMM, 15 DEF) had no HIV test after baseline; completeness of follow-up for HIV incidence was 91% (237/261 PY) for IMM and 89% (216/242 PY) for DEF. Three HIV infections were observed in IMM (1.3/100 PY); 19 infections were observed in DEF (8.9/100 PY) despite 174 prescriptions of post-exposure prophylaxis (PEP). This yields a rate difference of 7.6/100 PY (90%CI 4.1-11.2) and a relative reduction of 86% (62-96%; P=0.0002). The proportion with a confirmed STI indicative of condomless anal intercourse (rectal chlamydia/gonorrhoea) was similar in IMM (29%) and DEF (27%) (P=0.50).

Conclusions: In this high incidence cohort, daily TDF/FTC conferred impressive protection against HIV, and higher than the levels previously observed in the placebo-controlled trials. Concerns that effectiveness would be undermined in a real-world setting were unfounded. There was no evidence of an increase in STIs in this population, although they were frequently reported in the year before enrolment. This result strongly supports the use of PrEP among MSM who are at risk of HIV infection.

23LB On Demand PrEP With Oral TDF-FTC in MSM: Results of the ANRS Ipergay Trial

Jean-Michel Molina[1]; Catherine Capitant[2]; Bruno Spire[3]; Gilles Pialoux[4]; Christian Chidiac[5]; Isabelle Charreau[2]; Cecile Tremblay[7]; Laurence Meyer[2]; Jean-Francois Delfraissy[6]
And the ANRS Ipergay Study Group

[1]University of Paris Diderot, Paris, France; [2]Inserm SC10 US019, Villejuif, France; [3]Inserm U912, Marseille, France; [4]Hopital Tenon, APHP, Paris, France; [5]Hopital de la Croix Rousse, Lyon, France; [6]ANRS, Paris, France; [7]CHUM, Montreal, Canada

Background: Daily PrEP with oral TDF-FTC can reduce the risk of HIV infection in high risk individuals but long term adherence to a daily regimen remains challenging and explains the discordant results reported across trials. We wished to assess the efficacy of "on demand" PrEP in high risk MSM.

Methods: High risk adult MSM who reported condomless anal sex and had a creatinine clearance > 60 mL/mn were enrolled in this prospective randomized double-blinded placebo-controlled study. Participants (pts) were asked to take two pills of TDF-FTC (300mg/200mg per pill) or placebo 2 to 24h before each sexual intercourse, then another pill 24h later and a fourth pill 48h after the first drug intake. All subjects received risk-reduction counseling, condoms, HBV and HAV vaccines when needed, were informed about post-exposure prophylaxis and were regularly tested for HIV and other sexually transmitted infections (STIs). The primary study objective was to demonstrate a reduction in HIV incidence with on demand PrEP. In November 2014, following the DSMB recommendation, the placebo arm was discontinued and on demand PrEP was offered to all participants.

Results: From February 2012 to November 2014, 414 pts were randomized and 400 without HIV-infection were enrolled. After a median follow-up of 8.8 months (IQR: 4.3 to 20.5), the incidence of HIV-infection was 6.75 per 100 pt-years in the placebo arm and 0.94 per 100 pt-years in the TDF-FTC arm indicating a relative reduction of 86% in the incidence of HIV with on demand PrEP (95%CI: 39.4-98.5%, P=0.002). Sixteen pts acquired HIV-infection after enrollment, 14 in the placebo arm and 2 in the TDF-FTC arm. Pts used a median of

14 pills/month (IQR: 8-20). Overall, 34% of pts acquired a new STIs. Safety was good with only one pt discontinuing TDF-FTC because of suspected drug-drug interaction. The rate of serious adverse events was low (9%) and similar across the study arms. Drug-related gastrointestinal adverse events (nausea, diarrhea, abdominal pain) were reported more frequently with TDF-FTC than with placebo (13% vs 6%, p=0.02). Only 2 pts (1%) in the TDF-FTC arm had transient decreases in creatinine clearance < 60 mL/mn.

Conclusions: On demand PrEP with oral TDF-FTC is highly effective to reduce the incidence of HIV-infection in high risk MSM and has a good safety profile.

24 Near Elimination of HIV Transmission in a Demonstration Project of PrEP and ART

Jared Baeten[1]; Renee Heffron[1]; Lara Kidoguchi[1]; Nelly Mugo[2]; Elly Katabira[3]; Elizabeth Bukusi[2]; Stephen Asiimwe[4]; Jessica Haberer[5]; Deborah Donnell[6]; Connie Celum[1]

[1]University of Washington, Seattle, WA, US; [2]Kenya Medical Research Institute, Nairobi, Kenya; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]Kabwohe Clinical Research Centre, Kabwohe, Uganda; [5]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [6]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US

Background: Antiretroviral-based HIV prevention interventions, including pre-exposure prophylaxis (PrEP) and antiretroviral therapy (ART), showed high efficacy for HIV protection in clinical trials among African HIV serodiscordant couples. Assessing the effectiveness of these interventions, and their ability to complement one another, in implementation settings is a priority.

Methods: We are conducting the Partners Demonstration Project, an open-label, prospective study of PrEP and ART delivery among antiretroviral-naïve high-risk heterosexual HIV serodiscordant couples in Kenya and Uganda. High-risk couples are defined by a validated risk scoring tool (Kahle et al., JAIDS 2013). PrEP is offered as a 'bridge' to ART in the partnership – i.e., until ART initiation by the HIV-infected partner and for the first 6 months after ART is started; ART is recommended following national ART guidelines – initially CD4 <350 cells/μL but more recently all HIV serodiscordant couples regardless of CD4 count. To assess the impact of the PrEP as a bridge to ART strategy on HIV transmission, we compared observed HIV incidence to a counterfactual simulation model, using bootstrapping methods and constructed with data from a prior prospective study of HIV serodiscordant couples (the Partners PrEP Study, placebo arm), sampled selecting for a subset with an identical distribution of risk scores and duration of follow-up.

Results: Enrollment in the Partners Demonstration Project began in November 2012 and completed in August 2014, with a final sample size of 1013 couples. Given the risk score distribution of the study population, the counterfactual simulations predicted 21.7 HIV infections would be expected to date in this population (incidence 5.3 per 100 person-years, 95% CI 3.2-7.6). However, through July 2014, only one incident HIV infection has been observed during 440 person-years of follow-up, for an observed HIV incidence of 0.2 per 100 person-years (95% CI 0.0-1.3, p<0.0001 versus predicted) (Figure). PrEP was used during 47% of the 440 person-years of follow-up, ART 17%, both 25%, and neither 11%.The one transmission occurred in the absence of ART and with evidence of low PrEP adherence.

Conclusions: Early results from this demonstration project integrating time-limited PrEP and ART for HIV prevention in African couples show near elimination of HIV transmission, with an observed HIV incidence <0.5% per year compared to an expected incidence >5% per year.

25 Scale-Up of Preexposure Prophylaxis in San Francisco to Impact HIV Incidence

Robert M. Grant[3]; Albert Liu[2]; Jen Hecht[4]; Susan P. Buchbinder[2]; Shannon Weber[1]; Pierre-Cedric Crouch[4]; Steven Gibson[4]; Stephanie Cohen[2]; David Glidden[1]

[1]University of California San Francisco (UCSF), San Francisco, CA, US; [2]San Francisco Department of Public Health, San Francisco, CA, US; [3]Gladstone Institutes, San Francisco, CA, US; [4]San Francisco AIDS Foundation, San Francisco, CA, US

Background: Since 2007, rates of new HIV diagnoses in San Francisco (SF) decreased with widespread HIV testing, pooled HIV RNA testing for high-risk seronegatives, increased viral suppression rates, and grass-roots initiatives. Consumer demand for pre-exposure prophylaxis (PrEP) has increased since mid-2013. Local goals for PrEP scale-up have not been established.

Methods: A simple model was developed to forecast HIV transmission with expanded PrEP use. The model considers infectiousness and partnering practices of diagnosed and undiagnosed persons with HIV infection, viral suppression rates, and transmission to uninfected people having low, moderate, or high numbers of partners. Model parameters for SF were derived from surveillance, local research on seroadaptive behaviors, and SF-specific data from cohort studies, including the iPrEx Open Label Extension (OLE). Adherence in OLE was monitored by drug concentrations in dried blood spots and mapped to efficacy using global iPrEx data. The optimistic scenario assumes PrEP uptake will attract and retain people with higher exposure to HIV, as was observed at SF's OLE site. The realistic scenario assumes incidence rates that are typically observed in SF cohorts that did not include access to PrEP.

Results: In SF, the HIV diagnosis rate is 94% with 67% viral suppression. Among 150 eligible participants in OLE in SF, 64% chose to start PrEP; People starting PrEP were more likely to report non-condom receptive anal intercourse (44% vs 26%; P=0.03). Adherence yielded substantially protective drug concentrations among 96% of users through week 24, falling slightly afterward. If PrEP were used by 6400 people in the optimistic scenario (incidence 1.3 to 4.2/100py), the number of new infections could fall by 50% city-wide; doubling the number on PrEP could reduce new infections to less than 50 per year, a 86% reduction. In the realistic scenario (incidence 0.8 to 2.5/100 py), the city-wide incidence falls by 30% with 6400 people on PrEP; getting to less than 50 cases a year requires that diagnosis rates increase to over 99% with 90% viral suppression, at which point PrEP's impact on HIV incidence decreases because exposure to untreated HIV infection would be rare.

Conclusions: Demand for PrEP is increasing in SF with high rates of adherence. Widespread use of PrEP could markedly decrease new HIV infections, especially if synergies between PrEP uptake and adherence, HIV exposure, and HIV testing continue during PrEP rollout.

26LB FACTS 001 Phase III Trial of Pericoital Tenofovir 1% Gel for HIV Prevention in Women

Helen Rees[1]; Sinead A. Delany-Moretlwe[1]; Carl Lombard[2]; Deborah Baron[1]; Ravindre Panchia[4]; Landon Myer[3]; Jill L. Schwartz[5]; Gustavo F. Doncel[5]; Glenda Gray[2]
On behalf of the FACTS 001 Study Team

[1]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa; [2]South African Medical Research Council, Cape Town, South Africa; [3]University of Cape Town, Cape Town, South Africa; [4]Perinatal HIV Research Unit, Soweto, South Africa; [5]CONRAD, Arlington, VA, US

Background: HIV prevention in women is a major public health priority. Pericoital vaginal application of tenofovir (TFV) gel has been demonstrated to prevent male-to-female HIV transmission in a proof of concept phase IIB trial. However, adherence to product is a critical driver of microbicide effectiveness. Additional data are required for licensure.

Methods: FACTS 001 is a phase III, multi-centre, double-blind, randomised, placebo-controlled trial undertaken in 9 sites in South Africa which evaluated the safety and effectiveness of pericoital TFV 1% gel when using the BAT-24 regimen (before and after sex; no more than 2 doses in 24h). HIV-negative women aged 18-30 years received intensive counselling on product adherence and HIV risk reduction with condom provision. Monthly follow-up visits included HIV and safety testing, return of unused product and used gel applicators, and ongoing counselling on product adherence for up to 27 months. Product adherence was measured by proportion of self-reported sex acts covered by gel. In the primary intent-to-treat analysis, the effectiveness of TFV gel was assessed using a log-rank test stratified by site. A nested case-cohort substudy (n=214) also examined TFV drug levels in quarterly cervicovaginal lavage (CVL) samples in HIV seroconverters vs controls.

Results: Between Oct 2011 and Aug 2014, 3844 participants were screened, 2059 enrolled and 2029 included in the primary analysis. At enrolment, participant mean age was 23 years, most were unmarried (88%), lived with parents (62%), and had earned ⟨US$100 in the past 3 months (73%). 3036 person-years of observation were accrued and 7.4% of participants were lost to follow-up. Overall 123 HIV infections occurred (HIV incidence: 4.0/100 women years); 61 in the TFV arm and 62 in the placebo group (incidence rate

ratio [IRR], 1.0; 95% CI: 0.7-1.4). TFV gel effectiveness was highest in women who reported product use in 〉72% of sex acts (IRR 0.43; 95% CI 0.09-1.61); however, this subgroup represented only 20% of participants. In the case-cohort substudy, high TFV in CVL was significantly associated with a reduction in HIV acquisition (HR: 0.52; 95% CI: 0.27-0.99; p=0.04).

Conclusions: In this trial, pericoital vaginal TFV 1% gel was not effective in preventing HIV acquisition. In a stratified analysis, there was an association between adherence based on returned applicators and HIV effectiveness, and a significant association between TFV levels in CVL and reduction in HIV incidence.

27 Effect of Oral and Gel Tenofovir on Genital HSV Shedding in Immunocompetent Women

Rachel A. Bender Ignacio[1]; Tara Perti[2]; Amalia S. Magaret[1]; Sharanya Rajagopal[1]; Meei-Lee W. Huang[1]; Christine M. Johnston[1]; Stacy Selke[1]; Jeanne M. Marrazzo[1]; Anna Wald[1]

[1]University of Washington, Seattle, WA, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: Tenofovir is a potent anti-HIV agent with efficacy in studies of pre-exposure prophylaxis when taken orally or used as intravaginal gel. Recent studies suggest that tenofovir also reduces the risk of HSV-2 acquisition. Whether oral or gel tenofovir may be useful in HSV disease management, or to decrease HIV and HSV-2 transmission from co-infected persons, is unclear.

Methods: We randomized immunocompetent women with symptomatic HSV-2 infection 2:2:1 to oral tenofovir disoproxil fumarate (TDF)/placebo vaginal gel, oral placebo/tenofovir (TFV) vaginal gel, or double placebo in a one-way cross-over clinical trial. Women collected twice daily genital swabs for HSV PCR and completed symptom diaries during a 4-week lead-in and 5 week treatment phase. The primary intent-to-treat analysis was within-arm comparison of shedding rates and genital lesions with Poisson generalized linear mixed effects models and shedding quantity with a linear mixed-effects model.

Results: 73 women were enrolled and 64 completed the lead-in observation phase and were randomized: 24 women to TDF, 27 to TFV gel, and 13 to placebo. Relative to baseline, genital HSV shedding showed a small decrease from 22.9% to 19.5% (RR=0.86 p=0.09) in the TDF arm, but did not differ in the TFV gel arm (13.8% versus 12.0%; RR=0.94, p=0.54) or in the placebo arm (21.3% versus 20.4%; RR=0.90, p=0.45; Table 1). Asymptomatic shedding decreased in the TDF arm only (RR=0.74, p=0.01). There was no change in days with HSV lesions or number of shedding episodes. Shedding quantity decreased by 0.50 $\log_{10}$ copies in the TFV gel arm (p=0.008), but remained consistent in the TDF (p=0.18) and placebo arms (p=0.45). The per-protocol analysis included 20 women in the TDF arm, 20 in the TFV gel arm, and 9 in the placebo arm who completed 33 days of study product with 90% adherence. Relative to baseline, the shedding frequency was reduced in the TDF arm (RR=0.74, p=0.006), and quantity was reduced in the TDF (0.41 log) and TFV gel arms (0.6 log); other findings were similar to the full cohort. The TDF and TFV products were both well tolerated, and adherence was 97% by returned product count in all arms.

Risks of HSV-2 Shedding and Lesions by Study Arm

	Intent to Treat			Per protocol		
	Oral Tenofovir RR (p)	Gel Tenofovir RR (p)	Placebo RR (p)	Oral Tenofovir RR (p)	Gel Tenofovir RR (p)	Placebo RR (p)
Genital Shedding	0.86 (0.086)	0.94 (0.54)	0.90 (0.47)	0.74 (0.006)	0.95 (0.69)	0.78 (0.11)
Asymptomatic Shedding	0.74 (0.010)	1.30 (0.090)	0.75 (0.15)	0.69 (0.006)	1.38 (0.085)	0.73 (0.12)
Lesions	0.98 (0.90)	0.80 (0.25)	0.95 (0.82)	0.75 (0.032)	0.81 (0.15)	0.75 (0.11)
HSV quantity (change in $\log_{10}$ copies)	-0.16 (0.18)	-0.50 (0.008)	0.16 (0.45)	-0.41 (0.004)	-0.60 (0.003)	0.18 (0.42)

Conclusions: Oral TDF causes small reductions in shedding and lesion rate, and quantity of virus shed when used consistently. Vaginal TFV gel decreases shedding quantity by 60%. In contrast to evidence that oral and gel tenofovir may reduce HSV-2 acquisition, benefits in treatment of established HSV-2 infection are minimal.

28 Injectable Hormonal Contraception Use and Women's Risk for HSV-2 Acquisition

Mary K. Grabowski[1]; Ronald H. Gray[1]; Fred Makumbi[2]; Joseph Kagaayi[2]; Andrew D. Redd[3]; Fred Nalugoda[2]; Maria J. Wawer[1]; David Serwadda[4]; Thomas C. Quinn[3]; Aaron A. Tobian[5]

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]Rakai Health Sciences Program, Kalisizo, Uganda; [3]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US; [4]Makerere University College of Health Sciences, Kampala, Uganda; [5]Johns Hopkins University, Baltimore, MD, US

Background: Injectable hormonal contraception (HC) use has been associated with increased risk of HIV acquisition in women, but findings are inconsistent. The pathophysiology of how injectable HC use might increase HIV risk is unclear. Heightened risk for other sexually transmitted infections (STI) has been postulated as a possible mechanism, but it is unknown if injectable HC increases risk for other viral STIs. We assessed the association between oral and injectable HC use and incident herpes simplex virus type 2 (HSV-2), which is a risk factor for HIV acquisition.

Methods: Risk of incident HSV-2 associated with HC use was assessed among 682 HIV and HSV-2-negative women whose HIV-negative male partners were enrolled in a trial of medical male circumcision in Rakai, Uganda. Women were followed annually over two years. HSV-2 incidence was compared among women using injectable HC stratified into consistent, newly initiated, or discontinued use between visits, women using oral HC, pregnant women, and women who were neither pregnant nor using HC (referent group). Hazard ratios (HR) were estimated using discrete-time Cox proportional hazards models with adjustment for demographics, sexual behaviors, and condom use.

Results: We identified 70 incident HSV-2 events. Incidence was 13.1/100 person-years (py) among women consistently using injectable HC, and 3.9 and 5.2/100 py among women initiating and discontinuing injectable HC, respectively. Incidence was 2.8/100 py among oral HC users, while among non-HC users, incidence was 4.3/100 py in pregnant women and 6.6/100 py in non-pregnant non-HC using women. Compared to women who were neither pregnant nor using HC, the adjusted hazard ratio of HSV-2 acquisition among women consistently using injectable HC was 2.26 (95%CI: 1.09-4.69, p=0.029). Among 132 women with HSV-2 positive partners, incidence was 36.4/100 py in consistent injectable HC users and 10.6/100 py in women who were neither pregnant nor using HC (adjHR: 6.23; 1.49-26.3, p=0.012). There was no increased risk for HSV-2 among women who recently initiated or discontinued injectable HC, oral HC users, or pregnant women.

Conclusions: Our data suggest consistent use of injectable HC is associated with increased risk of HSV-2 acquisition. The findings may be relevant to the associations between HIV risk and use of injectable HC in some prior studies, and might indicate that injectable methods broadly affect the risk of viral sexually transmitted infections in women.

29 Effect of Financial Incentives on Linkage to Care and Viral Suppression: HPTN 065

Wafaa M. El-Sadr[1]; Bernard M. Branson[2]; Gheetha Beauchamp[3]; H. Irene Hall[2]; Lucia V. Torian[4]; Barry S. Zingman[5]; Garret Lum[6]; Rick Elion[7]; Theresa Gamble[8]; Deborah Donnell[3]

[1]ICAP at Columbia University, New York, NY, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [3]SCHARP, Fred Hutchinson Cancer Research Center, Seattle, WA, US; [4]New York City Department of Health and Mental Hygiene, New York, NY, US; [5]Montefiore Medical Center, University Hospital for Albert Einstein College of Medicine, New York, NY, US; [6]District of Columbia Department of Health, Washington, DC, US; [7]Whitman-Walker Health, Washington, DC, US; [8]FHI360, Durham, NC, US

Background: Enhancing the HIV continuum is critical. HPTN 065 evaluated the effect of financial incentives (FI) on linkage to care (L2C) and viral suppression (VS) in Bronx, NY (BNY) and Washington, DC (DC).

Methods: A total of 34 (16BNY/18DC) HIV test sites and 37 (20 BNY/ 17 DC) care sites were randomized to FI or standard of care. At FI test sites, HIV+ persons received coupons ($125) redeemable if care visit occurred within 3 months (M). At FI care sites, patients (Pts) on ART could earn $70 gift card per quarter with VS. Lab data reported to HIV Surveillance were used for primary site-level outcomes: for L2C, CD4 or VL within 3M of HIV+ test; for VS, VL<400 copies/ml in engaged Pts (≥2 visits in last 15 M); for continuity in care, CD4 or VL in 4 of prior 5 quarters. FI sites reported numbers of eligible Pts, coupons, and gift cards dispensed. GEE were used to compare FI and SOC outcomes (Figure).

Results: 1,346 HIV+ PTS (443 BNY/903 DC) were included in evaluation of L2C at 15 hospitals and 19 community sites: In BNY/DC, respectively, 66%/76% were men, 35%/49% MSM, 50%/70% Black, 46%/10% Hispanic; 20% <25 years in both cities. On average 15,780 Pts were in care (8,927 BNY/6,853 DC) at 17 hospitals and 20 community sites: 57%/74% were men, 19%/48% MSM, 47%/72% Black and 48%/6% Hispanic in BNY/DC. For L2C, 1,061 coupons (238 BNY/823 DC) were dispensed and 194 (82%)/644(78%) redeemed in BNY/DC. For VS, 9,641 Pts (5,275 BNY/4,366 DC) were potentially eligible for gift cards, 84% of 49,650 visits qualified for cards (81% BNY/87% DC) and 39,359 gift cards were dispensed (23,265 BNY/16,094 DC).

For L2C, FI did not significantly increase overall L2C above SOC (OR: 1.05, 95%CI: 0.69, 1.58, p0.83) and no effect was noted in subsets of sites. For VS, while FI did not significantly increase VS overall (3.9%, CI: −3.5%, 11.2%, p0.3), substantial increases were noted at hospital clinics (4.9%, CI: 0.9%, 8.9%, p0.02), smaller sites (≤185 patients in care) (9.6%, CI:1.2%,17.9%, p0.03), sites with lower VS at baseline (≤65%) (10.4%, CI: 2.0%,18.7%, p0.01) and at peak of intervention (5.5%, CI:0.6%,10.5%, p0.03). No difference was noted by city for L2C or VS. FI increased continuity of care by 8% overall (CI: 2.1%, 13.9%, p0.008), and at community clinics, smaller sites, and sites with higher baseline VS.

Endpoints	Effect of Financial Incentives compared to standard of care (95% confidence Intervals)	p-value
Linkage to Care (L2C) (Among newly diagnosed HIV+ or out of care HIV re-tester)	Increase in odds of linkage to care	
Linked to care within 3 months: N = 34 sites	1.05 (0.69, 1.58)	0.83
Viral Suppression (VS) (VL<400 copies/mL among patients in care at a site)	Increase in proportion of virally suppressed patients	
All patients in care: N = 37 sites	3.9% (-3.5%, 11.2%)	0.30
Peak of intervention (Q4 2012)	5.5% (0.6%, 10.5%)	0.031
Subgroups:		
Smaller clinics* (≤185 HIV-infected patients): N = 19	9.6% (1.2%, 17.9%)	0.025
Larger clinics*: N = 18	5.4% (-1.3%, 12.1%	0.11
Lower baseline VS (≤65% VS): N = 19	10.4% (2.0%, 18.7%)	0.015
Higher baseline VS: N = 18	2.4% (-5.9%, 10.8%)	0.57
Hospital-based clinics: N = 17	4.9% (0.9%, 8.9%)	0.016
Community clinics: N = 20	2.3% (-7.0%, 11.6%)	0.63
Continuity in care (Clinic visits in 4 of prior 5 quarters among patients in care)	Increase in proportion of patients with continuity of care	
All patients in care: N = 37 sites	8.0% (2.1%, 13.9%)	0.008
Peak of intervention (Q4 2012)	7.9% (2.5%, 13.4%)	0.006
Subgroups		
Smaller clinics* (≤185 HIV-infected patients): N = 19	23.1% (14.8%, 31.3%)	<0.001
Larger clinics*: N = 18	5.6% (-1.1%, 12.3%)	0.10
Lower baseline VS (≤65% HIV-infected VS): N = 19	8.1% (-3.2%, 19.5%)	0.16
Higher baseline VS: N = 18	8.7% (2.3%, 15.0%)	0.007
Hospital-based clinics: N = 17	6.5% (0.2%, 12.7%)	0.042
Community clinics: N = 20	10.0% (1.7%, 18.3%)	0.019

*size of clinic based on median number of patients engaged in care at baseline

Conclusions: FI did not increase L2C. However, use of FI for VS showed promising effectiveness for sites with fewer patients, lower VS and hospital-based clinics and offers potential for treatment as prevention.

30 Medical Male Circumcision of HIV-Infected Men Reduces Long-Term Penile HIV Shedding

Jordyn L. Manucci[1]; Godfrey Kigozi[3]; Mary K. Grabowski[2]; David Serwadda[3]; Ronald H. Gray[2]; Maria J. Wawer[2]; Fred Nalugoda[3]; Andrew D. Redd[4]; Thomas C. Quinn[4]; Aaron A. Tobian[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, DC, US

Background: Medical male circumcision (MMC) for HIV prevention in uninfected men is increasing. In HIV-infected men, MMC is safe and reduces genital ulceration and HPV acquisition. MMC of HIV+ men reduced male-to-female transmission in observational studies, but in a randomized trial MMC was associated with increased HIV transmission to female partners if couples resumed intercourse prior to wound-healing. HIV shedding from MMC wounds is detectable in 39% of HIV+ men during the wound-healing (weeks 1-4), but decreased to 2.6% at six weeks post-MMC. We assessed penile HIV shedding before and three months after MMC among HIV-infected men in Rakai, Uganda to determine whether low HIV shedding is sustained and might reduce female HIV exposures.

Methods: HIV shedding was evaluated among 160 self-reported antiretroviral therapy (ART)-naïve HIV-infected men using a lavage of 5 mL of phosphate buffered saline (PBS, pH=7.2) at the coronal sulcus immediately prior to MMC and at MMC three month postoperatively. Penile HIV-1 RNA viral levels (VL) were determined by reverse transcriptase polymerase-chain-reaction (RT-PCR) assay (Abbott Laboratories. Abbott Park, IL). Matched odds ratios (MOR) of detectable HIV-1 post-MMC relative to pre-MMC were estimated using conditional logistic regression. Differences in amount of HIV shedding (log_{10} copies/mL of lavage fluid) among those with detectable lavage were assessed using Wilcoxon-Mann-Whitney tests.

Results: HIV shedding among ART-naive men was detected in 8.8% (n=14/160) of men prior to surgery and in 1.9% (n=3/160) 3 months post-MMC (MOR=0.15, 95%CI=0.35-0.68, p=0.01). Among men with detectable HIV shedding at enrollment, the median HIV VL was 2.47 log_{10}/ml (IQR=2.19-3.10) compared to 2.20 log_{10}/ml (IQR=2.06-2.23) at month three post-MMC (p=0.20). In a sensitivity analysis of men with CD4 count >350 cells/uL, HIV shedding was detected in 7.2% (n=8/106) of men prior to surgery and in 1.9% (n=2/106) 3 months post-MMC (MOR=0.25, 95%CI=0.05-1.17, p=0.08).

Conclusions: Detectable penile HIV shedding is reduced by 85% three months after MMC in ART-naïve HIV+ men. The data suggest that MMC in HIV-infected men may reduce HIV exposure and potentially transmission to uninfected female partners after wound healing.

Session O-2 Oral Abstracts
Room 613

10:00 am – 12:00 pm

Prevention, Diagnosis, and Treatment of Pediatric HIV Infection

31LB PROMISE: Efficacy and Safety of 2 Strategies to Prevent Perinatal HIV Transmission

Mary Glenn Fowler[1]; Min Qin[2]; Susan A. Fiscus[3]; Judith S. Currier[4]; Bonus Makanani[5]; Francis Martinson[6]; Tsungai Chipato[7]; Renee Browning[8]; David Shapiro[2]; Lynne Mofenson[9]
On Behalf of the IMPAACT PROMISE Team

[1]Johns Hopkins University School of Medicine/Makerere University–Johns Hopkins University Research Collaboration, Baltimore, MD, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, US; [4]University of California Los Angeles, Los Angeles, CA, US; [5]Univ of Malawi, Blantyre, Malawi; [6]University of North Carolina Project–Malawi, Lilongwe, Malawi; [7]Univ of Zimbabwe, Harare, Zimbabwe; [8]NIAID/NIH, Bethesda, MD, US; [9]National Institute of Child Health and Human Development, Bethesda, MD, US

Background: There are limited **c**linical trial data comparing the efficacy and safety of antepartum (AP) antiretroviral (ARV) regimens for prevention of mother-to-child transmission (PMTCT) in women with high CD4 counts.

Methods: PROMISE 1077BF/1077FF is an ongoing, prospective, open-label randomized trial being conducted in 14 sites in Africa and India among HIV+ pregnant and postpartum women with high CD4 counts. The trial has 3 randomized components, assessing the maternal and infant efficacy and safety of ARV PMTCT strategies during 3 periods: pregnancy through 14 days postpartum; breastfeeding; and after MTCT risk is over. The AP component compared a zidovudine (ZDV)-based regimen (**Arm A:** AP ZDV + single-dose nevirapine (NVP) at delivery + tenofovir (TDF)/emtricitabine (FTC) tail) and two triple ARV regimens (**Arm B:** ZDV-lamivudine (3TC) + lopinavir/ritonavir (LPV-r); **Arm C:** TDF/FTC + LPV-r). Efficacy analyses using infant Roche 1.5 PCR, compared MTCT in Arm A to the pooled triple ARV arms. Safety analyses compared all 3 arms. Since Arm C was only open to all women in protocol Version 3 (V3), comparisons of Arms A and B included all women, but comparisons with Arm C only included those randomized under V3.

Results: On 11/4/14, the Data Safety Monitoring Board recommended release of interim AP data through 14 days post delivery. As of 9/10/14, 3529 pregnant women had enrolled, including 1230 women in V3, and 3234 live births had occurred. Baseline median maternal age was 26 years; 97% were black African; median enrollment gestational age was 26 weeks; 97% were WHO Clinical Stage I; median CD4 was 530 cells/uL and 58% had CD4 ≥500 cells/uL. The Table shows significantly reduced MTCT with triple ARVs during pregnancy compared to Arm A. There were no maternal deaths. We found significantly higher rates of Grade ≥2 maternal chemistry events and moderate adverse pregnancy outcomes with either triple ARV arm compared to Arm A; but no significant differences in very preterm delivery (VPTD) <34 weeks, very low birth weight (VLBW) < 1500 g, or early neonatal death between Arm A and either triple ARV arm. However, among 1229 enrollees in V3, ZDV/3TC+ LPV-r was associated with significantly lower risk of neonatal death or VPTD than TDF/FTC + LPV-r.

OUTCOME (N in analyses)	Arm A ZDV/NVP	Arm B ZDV/3TC/LPV-r	Arm C TRV/LPV-r	P Value*		
All women, N= 3523; (3240 1077BF; 283 1077FF)# (**Version** 3 (V3), N= 1229)	N=1543 (V3, N=413)	N=1541 (V3, N=410)	N=439 (V3, N=406)	A vs B	A vs C	B vs C
Infant HIV Infection Rates by Age 14 Days (N=3096)	1.8% (25/1386)	0.5% (7/1385)	0.6% (2/325)	Combined Triple ARV arms vs Arm A: **-1.28% (-2.11%. -0.44%)****		
≥Grade 2 Maternal AE[a] (**All women**, N=3015)	17.3% (261/1510)	21.1% (318/1505)	16.7% (69/412)	**0.008**	-	-
≥Grade 2 Maternal Chemistry AE (**All women**, N=3015)	1.3% (19/1510)	5.8% (88/1505)	4.4% (18/412)	**<0.001**	-	-
≥Grade 2 Maternal Chemistry AE (**V3 women**, N=1157)	0.8% (3/392)	4.7% (18/385)	2.9% (11/380)	-	**0.03**	0.26
Maternal Deaths (**All women**, N=3523)	0	0	0	-	-	-
Moderate Adverse Pregnancy Outcome[b] (**All women**, N=2821)	27.5% (389/1414)	40.0% (563/1407)	35.3% (124/351)	**<0.001**	-	-
LBW <2500 g (N=2679)	12.0% (161/1347)	23.0% (306/1332)	17.2% (57/332)	**<0.001**	-	-
PTD <37 weeks (N=2817)	13.1% (185/1411)	20.5% (288/1406)	19.4% (71/366)	**<0.001**	-	-
Moderate Adverse Pregnancy Outcome[b] (**V3 women**, N=982)	27.2% (91/334)	37.5% (123/328)	34.7% (111/320)	-	**0.04**	0.46
LBW <2500 g (N=935)	8.9% (28/315)	20.4% (65/319)	16.9% (51/301)	-	**0.004** -	0.30
PTD <37 weeks (N=1022)	13.5% (46/341)	19.7% (68/346)	18.5% (62/335)	-	0.09	0.77
Severe Adverse Pregnancy Outcome[c] (**V3 women**, N=965)	6.7% (22/329)	4.3% (14/322)	9.2% (29/314)	-	0.25	**0.02**
VLBW <1500 g (N=935)	0.3% (1/315)	0.6% (2/319)	2.0% (6/301)	-	0.06	0.17
VPTD <34 weeks (N=1022)	3.2% (11/341)	2.6% (9/346)	6.0% (20/335)	-	0.10	**0.04**
Infant Deaths by Age 14 Days (**All infants**, N=2851)	2.0% (28/1432)	1.2% (17/1419)	4.0% (15/373)	0.13	-	-
Infant Deaths by Age 14 Days (**V3 infants**, N=1036)	3.2% (11/349)	0.6% (2/346)	4.4% (15/341)	-	0.43	**0.001**

#1077BF and 1077FF refer to the breastfeeding (1077BF) and formula feeding (1077FF) protocol versions
*Fisher's Exact Test P-value (outcomes with P>0.05 for all 3 pairwise comparisons are not shown)
**MTCT difference (group sequential repeated confidence interval)
[a] Any ≥grade 2 Hem/Chemistry adverse event (AE) or ≥grade 3 Sign/Symptom or Pregnancy related diagnosis
[b] Low birth weight (LBW) <2500 g; Preterm delivery (PTD) <37 wks; Stillbirth; Birth defect
[c] Very low birth weight (VLBW) <1500 g; Very preterm delivery (VPTD) <34 wks; Stillbirth; Major birth defect.

Conclusions: These results provide the first clinical trial evidence to support the current WHO PMTCT recommendations for use of triple ARVs during pregnancy. The safety findings require further study.

32 Most Breastfeeding Women With High Viral Load Are Still Undiagnosed in Sub-Saharan Africa

David Maman[1]; Helena Huerga[1]; Irene Mukui[4]; Benson Chilima[2]; Beatrice Kirubi[5]; Gilles Van Cutsem[6]; Charles Masiku[7]; Elisabeth Szumilin[8]; Thomas Ellman[3]; Jean-François Etard[1]

[1]Epicentre/Médecins Sans Frontières, Paris, France; [2]3. Ministry of Health, Lilongwe, Malawi; [3]Medecins Sans Frontières, Cape Town, South Africa; [4]National AIDS and STDs Control Program, Nairobi, Kenya; [5]Médecins Sans Frontières, Nairobi, Kenya; [6]Médecins Sans Frontières, Cape Town, South Africa; [7]Médecins Sans Frontières, Lilongwe, Malawi; [8]Médecins Sans Frontières, Paris, France

Background: No study has assessed the proportion of HIV-positive pregnant or breastfeeding (PBF) women virally suppressed at population level. Furthermore, critical data assessing the cascade of care among PBF women are needed to inform program policy. We used data from three population surveys to assess these key indicators.

Methods: Three household based surveys of individuals age 15 to 59 took place between September 2012 and November 2013 in Ndhiwa (Kenya), Chiradzulu (Malawi) and Mbolongwane/Eshowe (South Africa). Following consent, all individuals were interviewed and tested for HIV. Women reported their pregnancy and breastfeeding status and the result of their last HIV test. All individuals found HIV-positive were tested for viral load and CD4, regardless of the ART status. At the time of the survey, PMTCT option A was implemented in Kenya, B+ in Malawi and B in South Africa. Infection during PBF was defined as a positive-HIV test among a PBF woman who was unaware of her status and reported a negative HIV test during Ante Natal Care (ANC).

Results: Among the 21,782 individuals eligible, 12,461 were women and of them, 11,550(92.7%) were included in the surveys. More women were PBF in Kenya (37.8%, 1,413/3,760) and in Malawi (33.8%, 1,444/4,275) than in South Africa (12.5%, 439/3,515). Among them, HIV prevalence ranged from 13.4% in Malawi to 22.2% in Kenya and 23.0% in South Africa. The proportion of PBF women with viral load<1,000copies/ml was higher in South Africa (63.4%;95%CI 65.5-72.3) and Malawi (72.3%; 95%CI 65.5-78.2) compare to Kenya (27.3%; 95%CI 22.5-72.3). Of the breastfeeding women with viral load >1,000copies/mL, 58.6% (95%CI 52.0-65.0) were not diagnosed for HIV at the time of the survey. This proportion was similar across sites (p=0.16).

A total of 103(4.1%) breastfeeding women were infected during pregnancy or breastfeeding. This proportion was higher in Kenya (6.5%) than in South Africa (4.3%) and Malawi (1.9%). These new infections accounted for 37.5% (95%CI 31.5-44.4) of the HIV-positive breastfeeding women with viral load>1,000 copies/ml.

Conclusions: Viral suppression at population level among PBF women ranged from 27 to 72%. Our analysis showed that the majority of HIV+ PBF women with viral load>1,000cp/mL were undiagnosed which could be partly due to infection after HIV testing at ANC. To identify those women and to prevent transmission or at least to ensure early diagnosis of their infants, repeated HIV-testing should be implemented until the end of breastfeeding.

33 Delayed HIV Detection in Infants Exposed to ARV Prophylaxis During Breastfeeding

Caroline C. King[1]; Julie A. Nelson[2]; Carrie Ziemniak[3]; Michael G. Hudgens[2]; Gerald Tegha[4]; Charles S. Chasela[5]; Denise J. Jamieson[1]; Deborah Persaud[3]; Charles M. van der Horst[2]; Athena P. Kourtis[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, US; [3]Johns Hopkins University, Baltimore, MD, US; [4]UNC Project, Lilongwe, Malawi; [5]University of Witwatersrand, Johannesburg, South Africa

Background: We reported on the effectiveness of 28 weeks of infant nevirapine or maternal antiretrovirals in preventing HIV transmission during breastfeeding from a randomized trial of 2369 mother-infant pairs: the Breastfeeding, Antiretrovirals and Nutrition (BAN) study. After counseling on breastfeeding cessation and stopping the antiretroviral intervention, 28 infections were detected from 29 to 48 weeks: 13 on infant nevirapine arm (n=852), 9 on maternal ARV arm (n=849), and 6 on control arm (n=668). To determine whether the infections detected after 28 weeks occurred during the breastfeeding and antiretroviral intervention phase but had delayed detection on the antiretroviral arms, we performed ultrasensitive HIV testing on stored infant PBMC specimens.

Methods: Infants in the BAN study were tested for HIV DNA via the Roche Amplicor 1.5 assay on whole blood at birth, 2, 12, 28 and 48 weeks, and, to narrow the window of transmission, dried blood spots from intervening visits were tested. For this substudy, ultrasensitive (droplet digital PCR) HIV testing was performed on infants with HIV infections first detected after 28 weeks and stored PBMC specimens at 24 weeks (n=9).

Results: All three infants tested on the infant nevirapine arm had detectable HIV DNA at 24 weeks, compared to 2 of 4 infants on the maternal ARV and 1 of 2 on the control arms. For infants with detectable HIV at 24 weeks, the median delay in detection between the ultrasensitive and routine assays was 18.3 weeks for the nevirapine arm, 15.4 weeks for the maternal arm, and 9.4 weeks for the control arm. There were no significant differences in maternal viral load or reported antiretroviral adherence between arms for the 9 infants with ultrasensitive testing. None of the 3 infants on the nevirapine arm harbored de novo nevirapine resistance mutations.

Ultrasensitive HIV DNA assay results on 9 infants who first tested HIV-positive by sensitive assay after reported breastfeeding cessation and stopping the postnatal ARV intervention by 28 weeks.

ID	Arm	Last breastfed (age in days)	BAN HIV-negative results, starting at 12-week visit* (age in days)	BAN first HIV-positive result* (age in days)	Ultrasensitive HIV DNA assay results on PBMC at 24-week visit. For detectable HIV DNA, pol copy per 106 PBMCs	Resistance testing of mother and infant (at 48-week visit)
1	Infant NVP	203	84, 203, 232, 260, 263	302	Detectable at 179 days 6.1 copies	No mutations
2	Infant NVP	196	85, 196, 254	321	Detectable at 167 days 4.1 copies 5.1 copies	K103N†
3	Infant NVP	199	85, 199, 227, 255	299	Detectable at 171 days 20.1 copies	No mutations
4	Maternal ARV	196	84, 196, 224, 252, 293	321	Undetectable at 167 days	No mutations
5	Maternal ARV	204	85, 204, 262	303	Detectable at 176 days 23.5 copies 15.4 copies	No mutations
6	Maternal ARV	197	84, 197	230	Undetectable at 169 days	No mutations
7	Maternal ARV	168	84, 196, 224	257	Detectable at 168 days 2.1 copies 7.5 copies	No mutations
8	Control	202	90, 202	240	Detectable at 174 days 20.0 copies 32.7 copies	No mutations
9	Control	172	88, 196, 225, 256	293	Undetectable at 168 days	No mutations

* Infant HIV testing during the BAN Study follow-up was done on whole blood collected at birth, 2, 12, 28 and 48 weeks with a qualitative Roche Amplicor 1.5 DNA PCR assay (Roche Molecular Systems, Pleasanton, CA, USA). For positive infants, the window of HIV transmission was later narrowed by testing dried blood-spot specimens from interim visits for HIV DNA by Roche DNA assay or RNA using Gen-Probe Aptima HIV-1 assay.

† Mutation seen in mother and infant.

Conclusions: Using an ultrasensitive assay, extremely low HIV DNA concentrations were detected in 6 of 9 (66%) infants up to 22 weeks earlier than by standard testing**.** The prolonged inability to detect HIV DNA of routine sensitive assays in the context of postnatal ARV prophylaxis suggests that early antiretrovirals restrict HIV replication sufficiently to lead to missed diagnosis. Late detection of HIV infections also suggests that repeated virologic testing beyond the WHO recommendation of 6 weeks after breastfeeding cessation is warranted. Ultrasensitive testing may allow for earlier antiretroviral treatment, which might modify establishment of HIV reservoirs.

34 Evaluation of the Alere q for Point-of-Care Early Infant HIV Diagnosis in South Africa

Nei-Yuan Hsiao[1]; Max Kroon[2]; Lorna Dunning[2]; Landon Myer[2]

[1]University of Cape Town, Cape Town, South Africa; [2]University of Cape Town, Cape Town, South Africa

Background: New point-of-care (POC) HIV molecular diagnostic tools could fundamentally alter early infant HIV diagnosis (EID) and management in resource-limited settings by reducing the time to initiation of antiretroviral therapy and promoting retention in care. However few technologies have been independently evaluated and data on new technologies are urgently required.

Methods: We investigated the analytic performance of the Alere q HIV1/2 POC assay in the laboratory setting by comparing the result with the local standard-of-care (SOC), Roche CAP/CTM HIV-1 qualitative PCR. Testing was conducted on routinely collected EID samples received at the public sector reference lab in Cape Town, South Africa between November 2013 and September 2014. Cycle threshold (CT) values from the Roche systm were used as measures of relative quantification.

Results: A total of 1065 HIV-exposed infants (median age, 47 days) undergoing SOC testing with final infant status available were included in the study. The first Alere q test resulted in an error for 60 samples (6%) but 70% of all errors were resolved with a second Alere q test. The performance of Alere q is shown in Table 1. Excluding errors, overall specificity was 100% (lower bound of 95% confidence interval [CI], 99.5%) and sensitivity was 96.8% (95% CI, 93.2%-98.8%). False negative samples had a median CT value of 32.8 on the SOC assay, higher than both the true positives (median CT, 24.2; p<0.001) and errors (median CT, 21.0; p<0.001). When analysis was restricted to specimens from newborns tested at <3 days of age, specificity remained high (100%) but sensitivity decreased to 91.6%.

		Roche CAP/CTM HIV-1 qualitative PCR		
		Positive	*Negative*	*Total*
Alere q POC PCR (first test)	*Positive*	185	0	185
	Negative	6	814	820
	Error	11	49	60
	Total	202	863	1065

Table 1. Performance of Alere q point-of-care test compared to Roche CAP/CTM HIV-1 qualitative PCR for early infant diagnosis, based on 1065 children with final infant HIV status available.

Conclusions: These results demonstrate good performance characteristics of this POC assay used for EID in the laboratory setting. While POC testing for EID may have particular utility in the context of birth testing within delivery facilities, the lower sensitivity of tests conducted within 3 days of birth require attention. Higher CT values were observed for false negative results, possibly due to lower levels of circulating virus during early infection. Further research is required to determine whether similar results can be achieved when this technology is implemented in clinical care settings, including for in birth testing.

35 Early ART and Sustained Virological Suppression Limits HIV Proviral DNA Reservoir: CHER Evidence

Helen A. Payne[1]; Sarah Watters[1]; Marvin Hsaio[2]; Robin Callard[1]; Abdel Babiker[3]; Mark F. Cotton[4]; Kennedy Otwombe[5]; Avy Violari[5]; Diana M. Gibb[3]; Nigel J. Klein[1]

[1]University College London, London, United Kingdom; [2]University of Cape Town, Cape Town, South Africa; [3]MRC Clinical Trials Unit at University College London, London, United Kingdom; [4]Stellenbosch University, Cape Town, South Africa; [5]University of Witswatersrand, Johannesburg, South Africa

Background: Improved understanding of HIV-1 proviral DNA latent reservoir formation and impact of ART-strategies on reservoir size can inform treatment strategies in paediatric HIV.

Methods: HIV-1 proviral DNA was measured from a substudy of 118 children from the Children with HIV Early Antiretroviral Therapy (CHER) trial where HIV-infected infants <12 weeks with CD4% ≥25% were randomised to early limited ART for 40 or 96 weeks or deferred ART. For Infants on deferred ART or following ART interruption after 40/96 weeks ART was started/re-started for clinical progression (CDC severe stage B/C disease) or CD4% <20%. HIV-1 proviral DNA was measured by quantitative PCR using DNA extracted from 384 cryopreserved PBMC samples taken 12-weekly from 40 to 252 weeks after a minimum of 24 weeks of ART. The effects on proviral DNA decline of early versus deferred ART and ART-interruption were investigated. Predictive factors for reservoir decline were explored including ART duration, enrolment CD4 and CD4 at 96 weeks, HIV serostatus and quantitative HIV-antibody at 84 weeks, baseline CMV viraemia, immunological phenotypes, enrolment viral load, viral load 9-12 months prior to proviral DNA measurement and total weeks continuous suppression below 400 copies/ml. The profiles of 5 children with undetectable proviral DNA measurements were also described.

Results: After a minimum 24 weeks of ART, 73 children starting early ART showed a trend towards less HIV-1 proviral DNA compared with 45 children on deferred ART: median 27 [IQR 8 – 51] versus 100 [48 – 202] copies of provirus per 10^5 PBMCs, p=0.08). Overall, reduced reservoir size and probability of developing an undetectable reservoir were strongly associated with earlier ART-initiation and longer continuous virological suppression (p-values all <0.0001). However patterns of decline varied despite continuous ART and apparent virological suppression. ART-interruption only modestly increased levels of proviral DNA (p=0.03). HIV serostatus did not correlate with reservoir size (p=0.92) but higher CMV DNA levels at enrolment were associated with an increased HIV reservoir (p=0.02). Four children with undetectable proviral DNA underwent ART-interruption as per CHER randomisation and exhibited HIV-1 viral resurgence.

Conclusions: These findings inform the interplay between clinical, immunological or virological factors involved in reservoir dynamics, and support the view that early-initiation of ART and sustained virological suppression are key to reservoir reduction.

36 Long-Term Outcomes of HIV-Infected Children Initiating NVP vs LPV/r-Based Treatment

Linda Barlow-Mosha[1]; Konstantia Angelidou[2]; Moherndran Archary[8]; Avy Violari[7]; Jane Lindsey[2]; Lynne Mofenson[3]; Patrick Jean-Philipe[5]; Paul E Palumbo[4]; Benjamin Chi[6]
On behalf of the IMPAACT P1060 Protocol Team

[1]Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]National Institutes of Health, Bethesda, MD, US; [4]Geisel School of Medicine at Dartmouth, Lebanon, NH, US; [5]Henry M. Jackson Foundation for the Advancement of Military Medicine, Rockville, MD, US; [6]University of North Carolina at Chapel Hill, Chapel Hill, NC, US; [7]University of Witswatersrand, Johannesburg, South Africa; [8]University of KwaZulu-Natal, Durban, South Africa; [9]IMPAACT, SilverSpring, MD, US

Background: IMPAACT P1060 demonstrated short-term superiority of lopinavir/ritonavir (LPV/r)-based ART over nevirapine (NVP) for the primary endpoint (stopping randomized treatment, virologic failure [VF] or death by 24 weeks) in HIV-infected children regardless of NVP exposure at birth. In contrast, those on NVP had marginally superior improvements in CD4% and growth (weight and height z-scores). Longer-term outcomes are presented.

Methods: HIV-infected ART-eligible infants and children (2m - 3y) from 6 African countries and India enrolled into 2 cohorts based on prior NVP exposure (PrNVP) and were randomized to initiate NVP or LPV/r (with zidovudine and lamivudine). The study DSMB recommended closing enrollment and unblinding cohorts with PrNVP (2009) and no PrNVP (2010) due to superiority of the LPV/r arm for the primary endpoint. Participants could switch regimens and continue in observational follow-up. Randomized and observational data were combined in intent-to-treat (ITT) analyses to investigate long-term trends in VF and death (Cox proportional hazards models) and CD4% and growth (generalized

estimating equations). Additional analyses were performed using marginal structural models (MSM) to account for treatment switching and censoring. Models were adjusted for demographics and HIV disease status at entry.

Results: 229 participants were randomized to NVP and 222 to LPV/r based ART. As of January 2014, 75% were still in follow-up (median follow-up 4.6 years [IQR: 3.7-5.7]). From their original randomization, 48% were still on NVP while 81% were still on LPV/r. Participants in the NVP arm had significantly shorter time to VF (adjusted hazard ratio [aHR]: 1.91, 95%CI: 1.37-2.65) but not death (aHR: 1.64, 95%CI: 0.72-3.75). Mean CD4% and weight z-scores were higher in the NVP arm at 1 year, by 1.5% and 0.23 respectively ($p<0.05$), while height z-scores were not significantly higher by 0.15 ($p=0.10$). By the second year of follow-up, differences were no longer statistically significant. Similar trends were observed in MSM models for all outcomes.

Conclusions: Long-term virologic suppression was superior in children on LPV/r-based ART compared to NVP-based regimens. Early modest gains in CD4% and growth associated with NVP were no longer statistically significant beyond 1 year after ART initiation. These findings further support the current WHO recommendation for LPV/r-based ART as first line therapy for HIV-infected children aged < 3 years.

37 Structural Cardiovascular Changes Are Reversible in HIV-Infected Children in Zambia and Uganda.

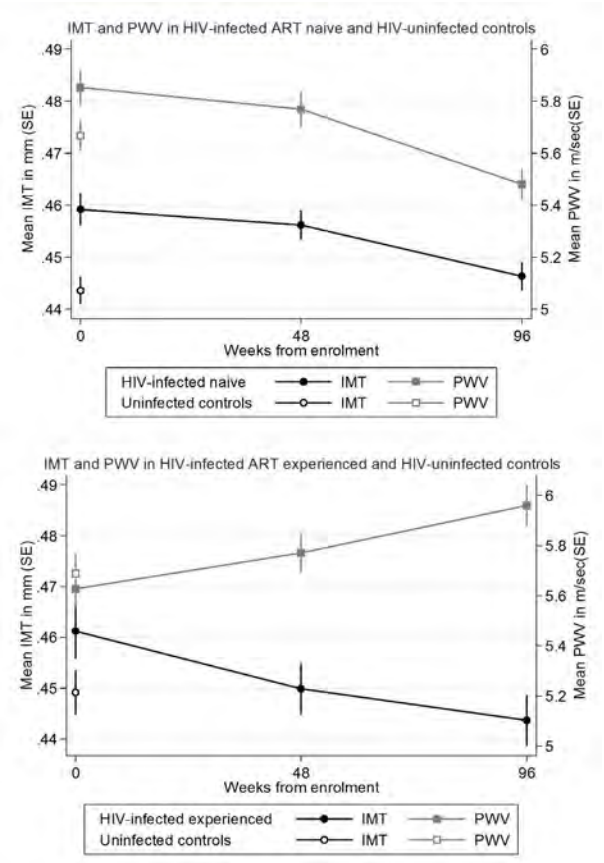
Julia M. Kenny[1]; Adrian Cook[1]; Grace Mirembe[2]; Dorica Masaku[3]; Priscilla Wavamunno[2]; Florence Odongo[2]; Alicja Rapala[1]; John Deanfield[1]; Diana M. Gibb[1]; Nigel J. Klein[1]

[1]University College London, London, United Kingdom; [2]Joint Clinical Research Centre, Kampala, Uganda; [3]University Teaching Hospital, Lusaka, Zambia

Background: Carotid intimal medial thickness (IMT) and pulse wave velocity (PWV), as measures of cardiovascular structure/function, are impaired in HIV-infected children in high-income countries. Few longitudinal data are available: none come from Africa where 90% HIV-infected children live.

Methods: ART-naïve and ART-experienced (on d4T+3TC+NNRTI for >2years, virologically suppressed at enrolment) HIV-infected children had IMT and PWV measured at baseline, 48 and 96 weeks within the CHAPAS-3 trial which evaluated d4T vs ZDV vs ABC-based first-line ART in Uganda/Zambia. Age-matched HIV-uninfected controls had a single assessment. Baseline differences between ART-naïve/experienced children vs controls, and longitudinal changes in HIV-infected children were compared using two-sample and paired t-tests respectively.

Results: In 208 ART-naïve children with median age 2.9y (IQR 1.7–4.4), median CD4% 18% (11-23) and 209 HIV-uninfected controls median age 3.0y (2.1–4.1), mean(sd) cIMT was 0.46(0.04) v 0.44(0.04)mm respectively ($p=0.0001$); PWV was 5.85(0.8) vs 5.67(0.74)m/sec respectively ($p=0.04$). Among 74 ART-experienced children on ART for mean 3.7y with median age 6.9y (5.9–8.50, median CD4% 33% (27-39) and 75 uninfected controls with median age 6.7y (5.6-8.6), mean(sd) cIMT was 0.46(0.05) vs 0.45(0.04)mm respectively ($p=0.09$); PWV was 5.63(0.61) vs 5.69(0.69)m/s respectively ($p=0.57$). In ART naïve children IMT and PWV significantly decreased from baseline (ART initiation) to week 96 mean(sd) cIMT -0.02(0.04)mm ($p=0.0001$), PWV -0.38(0.83)m/s ($p<0.0001$). In contrast whereas cIMT had significantly reduced by mean -0.2(0.06)mm ($p=0.01$) at week 96 in the ART experienced group PWV increased by 0.35(0.63)m/s ($p<0.0001$). There was no evidence that the changes differed by randomisation ART in either group ($p=0.6$).



Graph to show changes in IMT and PWV over 96 weeks in ART naive and ART experienced children with baseline data from age-matached HIV uninfected controls.

Conclusions: In this large study of arterial structural and function in HIV-infected children in Africa, ART-naïve HIV-infected children had significantly poorer IMT and PWV compared to age-matched controls but significant improvement seen after 96 weeks of ART. After a mean 3.7 years on ART, HIV-infected children had cIMT and PWV comparable to uninfected age-matched controls. IMT continued to improve after a further 96 weeks on ART. ART can reverse some of the structural/functional changes caused by HIV, strengthening the argument for early diagnosis and treatment of HIV-infected infants and children.

38LB ART With Weekends Off Is Noninferior to Continuous ART in Young People on EFV+2NRTI

Karina M. Butler
On behalf of the BREATHER Trial Team
Our Lady's Children's Hospital, Dublin, Ireland

Background: For HIV-1 infected young people (YP) facing lifelong ART, short cycle therapy (SCT) with long-acting agents offers the potential for drug-free weekends, less toxicity and better adherence, as well as cost savings.

Methods: BREATHER is a randomised, non-inferiority trial in Europe, Thailand, Uganda, Argentina & US. YP (>8, ≤24 yrs) on efavirenz (EFV)+2NRTIs and HIV-RNA (VL)<50c/ml for >12 months were randomised to continue daily ART (CT) or change to SCT (5 days on; 2 days off ART). Followup was for minimum 48 weeks, with 0, 4, 12, then 12 weekly visits. The primary outcome was the difference between arms in proportion with VL>50c/ml (confirmed) by 48 weeks, estimated using Kaplan-Meier method (12% non-inferiority margin) adjusted for region and age.

Results: 199 YP (11 countries) were randomised; 99 SCT, 100 CT and followed for median 86 weeks: 53% male, median age 14yrs (21% ≥18yrs); 35% Uganda site; 56% black, 19% Asian; 21% Caucasian; median CD4% 34%; CD4 count 793 cells/mm^3. By week 48, only one YP on CT was lost to followup. The SCT arm had 27% decreased drug exposure as measured by adherence questionnaire and a MEMs substudy showing median cap openings/week of 5 SCT vs 7 CT. By 48 weeks, 6 SCT vs 7 CT had confirmed VL>50c/ml; difference (90% CI) -1.2% (-7.3, 4.9); 2 SCT vs 4 CT had confirmed VL>400c/ml; difference 2% (-6, 2.0). All 6 SCT with VL>50c/ml resumed daily ART; 5/6 resuppressed, 3 on same regimen, 2 with switch; 2 others on SCT resumed daily ART for other reasons. Overall, 4 SCT vs 11 CT (p=0.1) changed ART regimen: 8 for toxicity, 4 simplification, 2 compliance and 1 VL failure. 7 YP (2 SCT, 5 CT) had major NNRTI mutations at VL failure; 2 (1 SCT, 1 CT) had M184V. 2 YP had new CDC B events (1 SCT, 1 CT). There were no significant differences in toxicity between SCT and CT: grade 3/4 AEs (8 vs 12), ART-related AEs (2 vs 8), SAEs (7 vs 6). At week 48, there was no evidence that SCT led to increased inflammation using an extensive panel of markers. YP expressed preference for SCT in a qualitative substudy and in pre- and post-trial questionnaires, particularly as it enabled weekend time with friends. 98% YP are in a 2-year followup extension of the trial.

Conclusions: Non-inferiority of VL suppression in YP on EFV-based firstline ART with VL<50c/ml was demonstrated for SCT vs CT, with similar resistance, safety and inflammatory marker profiles. Detailed evaluation of the immunological and virological impact of SCT is planned.

Session O-3 Oral Abstracts — Room 615

10:00 am – 12:00 pm

Cellular Dynamics, Sensing, and Viral Restriction

39 Envelope Trimer Numbers Required for Entry Steer HIV-1 Infectivity and Entry Kinetics

Oliver Brandenberg[2]; Carsten Magnus[2]; Peter Rusert[2]; Roland Regoes[1]; **Alexandra Trkola**[2]
[1]*ETH Zurich, Zurich, Switzerland;* [2]*University of Zurich, Zurich, Switzerland*

Background: The individual steps of the HIV entry process have been defined in detail. However, uncertainty prevails on the stoichiometric requirements of the entry process, namely the number of envelope trimers that need to be engaged to trigger membrane fusion. Here, we provide estimates of the HIV-1 entry stoichiometry utilizing a combined approach that incorporates experimental analyses and mathematical modeling.

Methods: To estimate the stoichiometry of entry (T) we analyzed pseudotyped virus stocks carrying mixed envelope trimers consisting of functional (wt) and dominant-negative mutant env, where a single dominant-negative env subunit incorporated into a trimer renders the trimer non-functional. Pseudovirus stocks expressing mixed trimers with different ratios of wt and dominant-negative env were produced in 293-T cells and virus infectivity determined by titration on TZM-bl reporter cells. Analysis of the data to derive estimates of T was performed using mathematical models we developed for this purpose. Virus entry kinetics were determined by a time-of-inhibitor addition experiment employing T-20 to stop virus infection of target cells at defined timepoints post-infection.

Results: Analysis of 11 divergent HIV-1 strains revealed that isolates differ in their requirements for trimer numbers during entry, with estimates ranging from 1 to 7 trimers and most isolates depending on 2 to 3 trimers to complete infection. Highlighting the biological relevance of our finding, a high entry stoichiometry proved to correlate with low virus strain infectivity and slow entry kinetics. This was confirmed studying the naturally occurring point mutation N160K in gp120 and by extensive analysis of mutant viruses lacking the V1V2 domain. In both cases changes in infectivity were reflected in different estimates of the entry stoichiometry compared to the matching wt envelopes.

Conclusions: While HIV can overcome partial envelope protein deficiencies by increasing the number of trimers involved in the entry process, this restricts infectivity to those virions that carry higher numbers of trimers, thereby reducing the overall infectivity of a virus population. Our data thus add an important concept to the growing body of information on molecular aspects of HIV entry and membrane fusion.

40 HIV-1 Accessory Protein Function: Evaluating VPU-Dependent Host Factor Degradation

Prashant Jain; Kevin Olivieri; Quy Nguyen; Paul De Jesus; Sumit Chanda
Sanford-Burnham Medical Research Institute, La Jolla, CA, US

Background: Cellular proteins called "restriction factors" are important in counteracting HIV-1 infection through cell intrinsic immune mechanisms. BST2 (Tetherin) is a cellular factor that prevents virion release by trapping HIV-1 on the plasma membrane. The HIV-1 accessory protein VPU is known to down-regulate BST2, thereby aiding in virion release. We hypothesize that VPU may target additional host factors to facilitate immune evasion. Here, we describe a 'High Content Imaging' based proteomic screen to identify host factors degraded by the HIV-1 VPU.

Methods: To identify novel host targets of VPU, 950 V5 tagged ISGs (Interferon Stimulated Genes), as well as VPU-Flag or a control LacZ-Flag were co-expressed in 293T cells. The cells were immunostained for V5 or Flag epitopes and imaged with Opera QEHS high content imaging microscope. Mean fluorescence intensity (MFI) for ISG-V5 was deduced in cells expressing either VPU-Flag or the LacZ-Flag. ISGs showing decreased MFI following VPU-Flag versus LacZ-Flag co-expression were considered as degraded by VPU.

Results: Following plate median normalization of fold change in V5 staining intensities, 10 host ISGs were identified as true hits for VPU dependent degradation. Confirmatory studies involving a secondary screen and immunoblot analysis of cell lysates confirmed the degradation of 6 ISGs identified in the primary screen. UBE2L6, an E2 ligase for ISG15 conjugation, was a primary hit and selected for downstream verification and functional analysis. Cross profiling ISG degradation following co-expression of HIV1 accessory proteins VPU, VIF and NEF, indicated a VPU specific degradation of UBE2L6. Importantly, we observed a significant and VPU dependent reduction in endogenous UBE2L6 as well as ISG15 conjugation in THP1 cells infected with HIV-1 VSVg wt or a VPU deficient HIV-1 VSVg. Our data indicates that HIV1 VPU modulates cellular ISG15 conjugation machinery by targeting the E2 ligase UBE2L6.

Conclusions: We describe a High Content imaging approach to identify novel host targets of HIV-1 VPU. Our results indicate that VPU targets multiple putative restriction factors for degradation. Elucidating the role of identified hits in counteracting HIV-1 infection would greatly enhance our understanding of VPU dependent enhancement of HIV-1 infection. Comprehensive understanding of virus dependent modulation of host immune machinery would significantly assist in developing effective anti-viral measures.

41 HIV-1 Adaptation to Humans Involved Interactions of Vpr With the DNA Damage Response

Oliver I. Fregoso; Michael Emerman

Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US

Background: The accessory protein Vpr is encoded by all extant primate lentiviruses and is important for viral replication *in vivo*. HIV-1 Vpr interacts with the host Cul4-DCAF1 ubiquitin ligase complex as well as the SLX4 complex of structure-specific nucleases, which have been implicated in the innate immune response. In addition, Vpr expression leads to G2 cell cycle arrest and activation of the DNA damage response after infection. We asked whether or not these functions of Vpr are related and what role adaptation of HIV-1 to humans played in shaping these interactions.

Methods: We cloned Vpr from a diverse array of primate lentiviruses. Through evolutionary analyses, we generated a phylogenetic framework of these Vpr isolates and tested them for their ability to interact with the human Cul4-DCAF1 complex and the human SLX4 complex by co-immunoprecipitation. We assayed for the ability of Vpr orthologs to activate the DNA damage response by immunofluorescence for DNA damage-associated foci and by cell-cycle analyses.

Results: We have identified that all Vpr orthologs are able to interact with the human Cul4-DCAF1 complex. Furthermore, we have found that a subset of these Vpr proteins can activate the DNA damage response in human cells. However, DNA damage induced by Vpr does not directly correlate with ability of Vpr to recruit the SLX4 complex. Instead, this function arose in select lentiviral lineages, including HIV-1 but not HIV-2.

Conclusions: The recruitment of Cul4-DCAF1 is a conserved ancestral function of Vpr and indicates that all Vpr orthologs have the potential to activate the DNA damage response in their hosts. As activation of the DNA damage response and SLX4 complex recruitment do not correlate, this indicates that Vpr activates host DNA damage response pathways through a still unknown mechanism. Moreover, our data suggests that recruitment of this complex occurred after the cross-species transmission of lentiviruses from chimpanzees to humans, and is therefore important for the adaptation of HIV-1 group M to humans.

42 The HIV-1 Protease Can Interact With RNA to Dramatically Enhance Its Activity

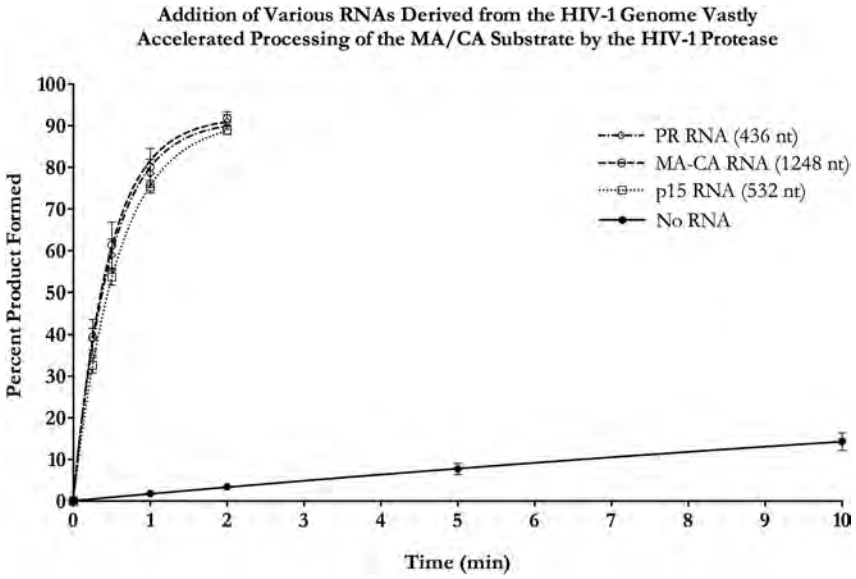
Marc Potempa[1]; Ellen Nalivaika[2]; Sook-Kyung Lee[1]; Celia A. Schiffer[2]; Ronald Swanstrom[1]

[1]*University of North Carolina, Chapel Hill, NC, US;* [2]*University of Massachusetts Medical School, Worcester, MA, US*

Background: In the maturation step of the HIV-1 lifecycle, the virus-encoded protease (PR) must process the structural polyprotein Gag to generate infectious virus particles. Previous reports found that cleavage of the p15NC maturation intermediate accelerates when RNA is present. Our studies have shown RNA-enhancement is substrate-independent. We hypothesize that enhancement results from an interaction between PR and RNA.

Methods: *In vitro* proteolysis reactions were performed +/- RNA with globular substrates derived from Gag or a 12-amino acid peptide. HIV PRs of multiple lineages were used to investigate whether RNA-enhancement is general to HIV. Alternative nucleic acids were also employed. Gel-shift assays were used to examine interactions between proteins and nucleic acids.

Results: Addition of RNA to two-substrate *in vitro* proteolysis reactions containing Gag derivatives p15NC and MA/CA accelerated cleavage of both substrates. In reactions with only MA/CA, the rate increased 80x (see figure). Cleavage of a peptide substrate, too small to interact with RNA and be simultaneously cleaved, was accelerated 20x. These data argue that RNA enhancement is substrate-independent. RNA enhanced the activity of Subtype B, C, and AE PRs; however, the HIV-2 PR was unaffected. Select short DNA oligonucleotides (~20 bases) capable of forming homomultimers could increase PR activity, but to a lesser degree than long, heteropolymeric RNA. The PR preferentially interacted with the multimeric forms of oligos in gel-shift assays, implicating the DNA complexes as necessary. Dimer stability is unaffected by RNA, since the tethered-dimer was equivalent to the wild-type PR in our assays. RNA lowered the K_m by 5-10x, and raised the V_{max} 2-5x.



Conclusions: RNA can directly interact with HIV-1 PRs *in vitro*, dramatically increasing their catalytic activity. This interaction likely relies on electrostatic forces, rather than sequence, since multimer formation was the principle determinant of effectiveness for DNA oligonucleotides. Mechanistically, RNA likely affects PR function post-dimerization, since RNA equivalently enhanced the wild type and tethered-dimer PRs. The differences in K_m and V_{max} show that RNA increases the PR's affinity for its substrate and its turnover capacity. These data raise the possibility that PR cleavage during assembly is regulated in part by the juxtaposition of the viral PR and virion-packaged RNA.

43 PQBP1 Is a Retrovirus-Specific Sensor Mediating cGAS/IRF3-Dependent Innate Responses

Sunnie M. Yoh[1]; Monika Schneider[1]; Stephen Soonthornvarcharin[1]; Rana Akleh[1]; Kevin Olivieri[1]; Paul De Jesus[1]; Chunhai Ruan[2]; Elisa de Castro[3]; Pedro Ruiz[1]; Adolfo Garcia-Sastre[3]
[1]Sanford-Burnham Medical Research Institute, La Jolla, CA, US; [2]University of Michigan, Ann Arbor, MI, US; [3]Icahn School of Medicine at Mount Sinai, New York, NY, US

Background: Infection of dendritic cells (DCs) by HIV-1 triggers an innate immune response that has been shown to be mediated through a cyclic GAMP synthase (cGAS)/IRF3-dependent pathway. We hypothesized that this pathway was activated by a cellular factor that recognizes a retrovirus-encoded molecular feature upstream of cGAS/IRF3. In an attempt to identify this proximal sensor of a HIV-1 pathogen-associated molecular pattern (PAMP), we performed a targeted RNAi screen utilizing primary human monocyte-derived DCs (MDDCs) and identified the protein PQBP1 as an innate immune sensor for HIV-1 DNA in myeloid cells.

Methods: We utilized human MDDCs to perform a sub-genomic RNAi screen of putative nucleic acid-binding proteins to identify cellular factors required for the innate response to HIV-1 infection. Screening "hits" were further assayed for their ability to directly associate with HIV-1 nucleic acids in infected MDDCs. PQBP1 was the only molecule found to be required for both innate signaling and that associated with HIV-1 nucleic acids. PQBP1 was subjected to extensive validation using reconstituted stable shRNA and CRISPR cell lines, measurement of cellular cGAMP levels, *in vivo* and *in vitro* DNA binding assays and characterization of protein interactions.

Results: Through our analysis, we demonstrated that PQBP1 directly binds to reverse transcribed HIV-1 DNA, and that it interacts with cGAS to initiate an IRF3-dependent innate response in myeloid cells. Further analysis revealed that PQBP1 associates with HIV-1 DNA through its C-terminus, but that it requires an intact WW-domain to associate with cGAS. Our study indicates that PQBP1 specifically recognizes a restricted set of retrovirally encoded DNA PAMPs, possibly originating from the secondary structure of RT intermediates.

Conclusions: The ability to recognize invariant microbial features, and not pathogen specific elements, such as DNA sequence, is the definition of a pattern recognition receptor (PRR), and our evidence suggests that PQBP1 falls into this category. Our study presents a molecular understanding of how HIV-1 is recognized by professional antigen presenting cells to trigger cell-autonomous antiviral responses to promote adaptive immunity. Identification of PQBP1 as a direct sensor of retroviral DNA provides an opportunity for development of pharmacological agonists that may potentially improve HIV vaccine efficacies.

44 Mucosal HIV-1 Transmission Specifically Selects for Type 1 Interferon-Resistant Viruses

Shilpa Iyer[1]; Frederic Bibollet-Ruche[1]; Christiana M. Shaw[1]; Weiyu Zhang[1]; Yingying Li[1]; Timothy Decker[1]; George M. Shaw[1]; Persephone Borrow[2]; Beatrice H. Hahn[1]
[1]University of Pennsylvania, Philadelphia, PA, US; [2]University of Oxford, London, United Kingdom

Background: Mucosally transmitted founder (TF) HIV-1 are more resistant to the antiviral effects of type 1 interferons (IFNs) than viruses that predominate during chronic infection. To determine whether IFN-resistant viruses are specifically selected for during HIV-1 transmission, we derived viral isolates by limiting dilution from both plasma and genital fluids of chronically infected transmission donors and examined their relative IFN resistance.

Methods: Plasma and cervicovaginal lavage (CVL) were collected from the donors of epidemiologically linked transmission pairs. Plasma or the non-cellular fraction of CVL samples were incubated with activated CD4+ T-cells to generate limiting-dilution isolates. Half genome sequences were analyzed to characterize the extent of genetic diversity. IFNα sensitivity of each isolate was analyzed by determining the IC50 in primary CD4+ T-cells.

Results: We first used plasma from patient CH212 to determine that 500-1000 vRNA copies were required to obtain limiting dilution isolates. The diversity among 18 CH212 isolates was 2.5%, comparable to that observed by SGS analysis of the plasma vRNA. We determined the IFNα sensitivity of each virus isolate. IC50 values ranged from 8 to 115 U/ml and were significantly lower than the IC50 value of the TF virus (240 U/ml) of the CH162 recipient. In an attempt to isolate IFNα-resistant viruses from the plasma, the limiting dilution isolation method was repeated in the presence of IFNα. The IFNα IC50 values of the 5 new isolates ranged from 155 to 225 U/ml, revealing that IFNα resistant viruses are present, but infrequent, in the donor plasma. We next obtained limiting-dilution isolates from plasma (n=10) and matching CVL (n=10) from donor CH492. The mean genetic diversity and the mean IFNα IC50 values were comparable between isolates derived from plasma and genital secretions. Interestingly, one CVL-derived isolate had a significantly higher IFNα IC50 value and was genetically most closely related to the single TF identified in the CH427 recipient.

Conclusions: Viruses circulating in plasma and sexual secretions of chronically infected individuals exhibit a wide range of IFN resistance, and are generally more IFN sensitive than TF viruses that establish de novo infections. However, some donor viruses exhibit elevated resistance to IFNα and seem to be those that are preferentially transmitted. Thus, IFN-resistant viruses are specifically selected from a pool of biologically diverse viruses during mucosal HIV-1 transmission.

45 The Dynamics of HIV-1 RNA Near the Plasma Membrane During Virus Assembly

Luca Sardo; Steven C. Hatch; Jianbo Chen; Olga A. Nikolaitchik; Ryan C. Burdick; De Chen; Christopher J. Westlake; Stephen Lockett; Vinay K. Pathak; Wei-Shau Hu
Frederick National Laboratory for Cancer Research, Frederick, MD, US

Background: HIV-1 must package its RNA genome to generate infectious particles. The interactions between viral RNA elements and the structural protein Gag are essential for efficient virus particle assembly. However, little is known about the dynamics and the events that lead to RNA packaging in living cells. We investigated 1) the window of opportunity for HIV-1 RNAs near the plasma membrane to interact with Gag and be packaged into viral particles, and 2) quantified the proportion of HIV-1 RNAs that, after reaching the plasma membrane, were packaged into assembling viral particles.

Methods: We labeled HIV-1 RNA with an RNA-binding protein fused to EOS, a photoconvertible protein whose fluorescence switches from green to red upon exposure to near-UV light. We selectively converted EOS near the plasma membrane of HeLa cells and followed the RNA signals over time by using total internal reflection fluorescence (TIRF) microscopy.

Results: In the absence of Gag, most of the HIV-1 RNAs stayed near the plasma membrane transiently, with ~50% of the RNAs departing within ~2 minutes; however, a portion of the RNAs (~20%) were detectable 30 minutes later. The presence of HIV-1 Gag increased the RNA retention time near the plasma membrane; most of the RNAs (~60%) were detected after 30 minutes. By tagging HIV-1 Gag with a blue fluorescent protein we observed that in the early phase of HIV-1 expression, when few or no Gag puncta are detected, ~10-40% of the HIV-1 RNAs that reached membrane were recruited into assembling particles.

Conclusions: These studies are the first measurements of HIV-1 RNA dynamics at the plasma membrane and the efficiency of RNA recruitment, which provide insights into the events leading to the generation of infectious HIV-1 virions.

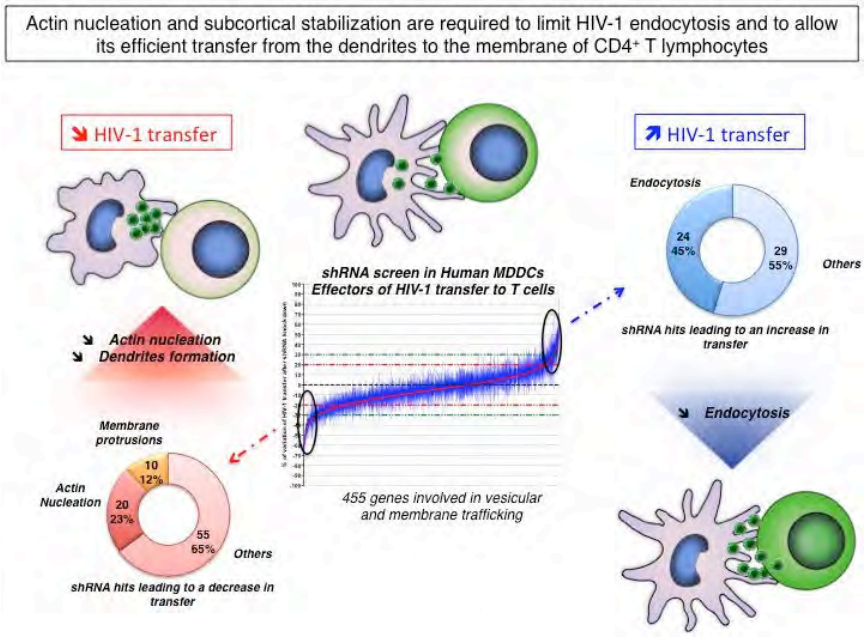
46LB Mechanisms of Dendritic Cell-Mediated Transfer of HIV-1 to CD4$^+$ T Lymphocytes

Mickael M. Menager[1]; Wendy Lin[1]; Jarrod S. Johnson[2]; Kristen Dancel-Manning[1]; Nicolas Manel[3]; Feng-Xia Liang[1]; Dan R. Littman[1]
[1]Skirball Institute of Biomolecular Medicine, New York, NY, US; [2]Seattle Biomedical Research Institute, Seattle, WA, US; [3]Institut Curie, Paris, France

Background: Dendritic cells (DCs) have essential roles in early detection of pathogens and in subsequent activation of both innate and adaptive immune responses, and are likely to be of critical importance in developing new strategies for protective HIV-1 vaccination. Whereas human DCs are resistant to productive viral replication, they have a unique ability to take up virus and transmit it efficiently to T lymphocytes. By doing that, the virus may evade, at least in part, the first line of defense of the immune system in mucosal tissues, exploiting DCs instead to facilitate rapid infection of a large pool of immune cells.

Methods: To gain insight into this cell biological process, we have used small hairpin RNA (shRNA) technology in primary monocyte-derived DCs (MDDCs) to suppress the expression of several hundred genes and analyze the impact on transfer of HIV-1 from DCs to T cells.

Results: By combining flow cytometry with confocal and electron microscopy experiments, we have identified and validated the function of TSPAN7 and DNM2 in viral transfer. These proteins appear to be involved in the control of actin nucleation and stabilization, which are important in limiting HIV-1 endocytosis and maintenance of virus on dendritic processes for efficient transfer to T lymphocytes. The requirement for actin nucleation and dendrite formation in HIV-1 transfer is strongly supported by 28 additional genes identified in the shRNA screen. Conversely, knock down of 24 genes linked to different types of endocytosis resulted in increased HIV-1 transfer.



Conclusions: This genetic approach is a first step towards a better understanding of the molecular and cell biological aspects of HIV-1 transmission between DCs and T lymphocytes, which is needed to evaluate the importance of this process in infected individuals. This approach should provide new tools and new targets for the design of therapies that limit viral replication and boost innate immune responses to control HIV dissemination.

Session O-4 Oral Abstracts
Room 6D

10:00 am – 12:15 pm

New Discoveries in HIV Pathogenesis

47 Inflammation Persists Despite Early Initiation of ART in Acute HIV Infection

Netanya S. Utay[1]; Jintanat Ananworanich[2]; Suteera Pinyakorn[3]; Adam Rupert[5]; Duanghathai Sutthichom[3]; Suwanna Puttamaswin[3]; Bonnie M. Slike[2]; Nelson L. Michael[2]; Daniel C. Douek[4]; Irini Sereti[4]

[1]University of Texas Medical Branch at Galveston, Galveston, TX, US; [2]US Military HIV Research Program, Silver Spring, MD, US; [3]South East Asia Research Collaboration with Hawaii, Bangkok, Thailand; [4]National Institutes of Health (NIH), Frederick, MD, US; [5]Leidos Biomedical Research, Inc, Frederick, MD, US

Background: Biomarkers of microbial translocation, inflammation, coagulation and fibrosis predict morbidity and mortality in patients with chronic HIV infection. The effects of starting antiretroviral therapy (ART) in patients with acute HIV infection (AHI) on levels of these biomarkers in chronic treated infection are unknown and may illuminate the potential impact of early ART on clinical outcomes.

Methods: Subjects were diagnosed with acute HIV infection and initiated ART within 0-5 days per RV254 protocol. Plasma levels of D-dimer, C-reactive protein (CRP), hyaluronic acid (HA), soluble CD14 (sCD14) and intestinal fatty acid binding protein (I-FABP, a marker of enterocyte turnover) were measured by ELFA (D-Dimer), Mesoscale (CRP) and ELISA (HA, sCD14, I-FABP) from 109 HIV-uninfected (HIV-) and 78 AHI Thai participants at diagnosis (week 0), weeks 2, 12, 24, 36, 48 and 96. Median values were compared between HIV+ and HIV- groups by Mann-Whitney test and longitudinal within-group comparisons by Wilcoxon matched-pairs signed rank test.

Results: Median age was 28 years (range 24-33) for HIV+ subjects and 27 years (22-37) for HIV- subjects. 92.3% of HIV+ subjects and 77.1% of HIV- subjects were male. Median time since HIV acquisition was 16 days (12-22), CD4 T-cell count 384 (293-525) cells/mm^3 and HIV RNA 5.6 (5.1-6.3) $\log_{10}$ copies/mL. Twenty subjects were diagnosed in 4th generation (4thG) stage 1 (median 12 days post-acquisition), 15 in stage 2 (16 days) and 43 in stage 3 (18 days). All week 0 biomarker levels were significantly higher in HIV+ than HIV- subjects (see table). I-FABP increased by week 2 and remained elevated regardless of 4thG stage. Other biomarkers did not decrease in individuals diagnosed in 4thG1 until week 12. sCD14, CRP and HA decreased by week 2 in individuals diagnosed in 4thG2, and sCD14, CRP, HA and D-dimer decreased by week 2 in individuals diagnosed in 4thG3. HIV+ subjects had significantly higher levels of all biomarkers except D-dimer after 48 and after 96 weeks of ART compared to HIV- subjects.

	Week 0		Weeks Since HIV Diagnosis (*P* compared to day 0)					
	HIV- (N=109)	HIV+ (N=78)	2 (N=77)	12 (N=75)	24 (N=75)	36 (N=71)	48 (N=62)	96 (N=32)
I-FABP (pg/mL)	701	984 *P*=0.0115	2746 *P*<0.0001	2625 *P*<0.0001	1837 *P*<0.0001	2287 *P*<0.0001	2797 *P*<0.0001	2254 *P*<0.0001
sCD14 (µg/mL)	0.78	1.53 *P*<0.0001	1.32 *P*=0.0046	1.17 *P*<0.0001	1.15 *P*<0.0001	1.05 *P*<0.0001	1.04 *P*<0.0001	1.16 *P*<0.0001
CRP (µg/mL)	0.26	1.35 *P*<0.0001	0.77 *P*=0.0009	0.51 *P*=0.0001	0.45 *P*<0.0001	0.41 *P*<0.0001	0.36 *P*=0.0001	0.49 *P*=0.0047
D-dimer (µg/mL)	0.17	0.28 *P*<0.0001	0.23 *P*=n.s.	0.15 *P*<0.0001	0.16 *P*<0.0001	0.16 *P*<0.0001	0.17 *P*<0.0001	0.18 *P*=0.0004
Hyaluronic acid (ng/mL)	9.00	18.39 *P*<0.0001	10.21 *P*=0.0030	12.55 *P*<0.0001	18.89 *P*=n.s.	16.29 *P*=0.0410	15.94 *P*=0.0019	11.94 *P*=0.0043

Levels of biomarkers of microbial translocation, inflammation, coagulation and fibrosis

Conclusions: Enterocyte turnover increases after initiation of ART during acute infection and persists into chronic infection. Biomarkers of inflammation, microbial translocation and fibrosis decrease, but remain elevated compared to HIV- controls with the exception of D-dimer. Together, these data suggest that the inflammatory damage caused by HIV may not be completely prevented by starting ART during acute HIV infection

48 HIV Burden and Biomarker Associations With Colonic HIV RNA During Acute HIV Infection

James L. Fletcher[2]; **Trevor A. Crowell**[1]; Robin Dewar[3]; Irini Sereti[4]; Bonnie Slike[1]; Nitiya Chomchey[2]; Rungsun Rerknimitr[5]; Nelson L. Michael[1]; Nicolas Chomont[6]; Jintanat Ananworanich[1]
RV254/SEARCH010 Study Group

[1]US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, US; [2]SEARCH, Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [3]Virus Isolation and Serological Lab, National Cancer Institute at Frederick, Frederick, MD, US; [4]National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, MD, US; [5]Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [6]Vaccine and Gene Therapy Institute Florida, Port St. Lucie, FL, US

Background: The colonic mucosa is typically one of the first sites infiltrated during acute HIV infection (AHI), becoming an important reservoir for the virus and a barrier to cure. We investigated virologic and immunologic correlates of detectable colonic HIV RNA during AHI.

Methods: Subjects were prospectively enrolled and offered ART during AHI (Fiebig stages I-V) from May 2009 to March 2012 in Bangkok, Thailand. Sigmoidoscopy was performed to collect colon tissue. Subjects were categorized by detectable (≥50 copies/mg) or undetectable HIV RNA in colonic mucosal tissue cells using homogenized biopsy specimens and the Siemens Quantiplex HIV-1 3.0 assay. Biomarkers and HIV burden in multiple compartments were compared between groups using the Mann-Whitney U test.

Results: From 49,458 samples screened for HIV, 75 individuals were enrolled during AHI and 42 consented to optional colon biopsy and are included in this analysis. The median age was 29 and 93% were male. Colonic HIV RNA was detectable in 32 subjects (76%).

As compared to subjects without detectable colonic HIV RNA, those with detectable HIV RNA tended to be in a later Fiebig stage (19% Fiebig I in detectable group vs. 70% Fiebig I in undetectable group, p=0.04); had a longer reported duration since HIV exposure; had higher median levels of IP-10, TNF-RII and neopterin; and had higher expression of HLA-DR/CD38 and Ki-67 on CD8 cells in both blood and colon (Table 1). Median CD4 count in mucosal mononuclear cells was lower in volunteers with detectable colonic HIV RNA. Detectable colonic HIV RNA was also associated with higher HIV RNA levels in the peripheral blood and cerebrospinal fluid as well as higher levels of both total and integrated HIV DNA in both the peripheral blood and colon.

Among subjects with baseline detectable colonic HIV RNA, 23 of 26 tested (88%) were undetectable after 24 weeks of ART. The eight tested subjects who were undetectable at baseline remained undetectable.

Table 1. Characteristics of Subjects during Acute HIV Infection, Stratified by Colonic HIV RNA

Characteristic	Colonic HIV RNA ≥50 copies/mg [N=32]	Colonic HIV RNA <50 copies/mg [N=10]	p
	Median (IQR)	Median (IQR)	
Age (years)	29 (24 – 31)	28 (25-42)	**0.62**
Time since HIV exposure (days)	16 (14 – 22)	11 (8 – 16)	**0.02**
Peripheral Blood			
CD4 (cells/mm^3)	391 (339 – 564)	491 (311 – 565)	0.67
CD8 (cells/mm^3)	624 (409 – 1105)	421 (271 – 500)	**0.03**
CD4:CD8 ratio	0.56 (0.38 – 1.17)	1.14 (1.12 – 1.45)	**0.01**
HLA-DR/CD38 expression on CD4 (%)	2.6 (1.8 – 4.3)	1.9 (1.4 – 2.4)	0.06
HLA-DR/CD38 expression on CD8 (%)	14.3 (9.5 – 16.9)	7.6 (5.7 – 11.7)	**0.01**
Ki-67 expression on CD4 (%)	1.8 (1.3 – 3.0)	1.8 (1.2 – 2.8)	0.92
Ki-67 expression on CD8 (%)	2.9 (2.2 – 5.5)*	1.6 (1.3 – 2.8)	**0.01**
HIV-RNA (log_{10}copies/mL)	5.6 (5.4 – 6.6)	4.3 (3.4 – 5.4)	**<0.01**
Total HIV DNA (copies/10^6 PBMC)	145 (9 – 1056)	8 (0 – 74)	**0.05**
Integrated HIV DNA (copies/10^5 PBMC)	2 (0 – 69)	0 (0 – 0)	**0.01**
IP-10 (pg/mL)	477.2 (205.6 – 727.2)	148.5 (68.3 – 350.9)	**0.02**
TNF-RII (pg/mL)	1062.1 (739 – 1771.4)*	649.3 (581.1 – 793)	**<0.01**
Neopterin (pg/mL)	2418.1 (1746.5 – 3137)	1367.6 (866.3 – 1910.3)	**0.01**
Colon			
CD4 (x10^6 cells/gm)	6.7 (2.2 – 9.9)	14.1 (7.6 – 18.2)	**0.05**
HLA-DR/CD38 expression on CD4 (%)	2.6 (2.0 – 3.4)	2.4 (0.9 – 3.4)	0.22
HLA-DR/CD38 expression on CD8 (%)	8.9 (5.5 – 13.4)	4.5 (3.2 – 6.0)	**0.01**
Ki-67 expression on CD4 (%)	8.5 (3.8 – 11.1)	2.4 (1.9 – 3.2)	**<0.01**
Ki-67 expression on CD8 (%)	13.5 (8.2 – 20)*	3.9 (3.4 – 8.2)	**<0.01**
Total HIV DNA (copies/10^6 cells)	477 (68 – 1610)	0 (0 – 29)	**0.01**
Integrated HIV DNA (copies/10^6 cells)	116 (0 – 425)	0 (0 – 0)	**0.03**
Cerebrospinal fluid			
HIV-RNA (log_{10}copies/mL)	3.9 (3.1 – 4.5)	1.8 (1.7 – 2.1)	**<0.01**

Characteristics of Subjects during Acute HIV Infection, Stratified by Colonic HIV RNA

Conclusions: This study highlights the rapidity and breadth of viral infiltration during AHI. Detectable colonic HIV RNA is common and correlates with increase HIV burden in the peripheral blood, colon, and CSF. Subjects with detectable colonic HIV RNA during AHI demonstrate colonic CD4 depletion, peripheral inflammation, and CD8+ T-cell activation in both colon and periphery. Subjects with undetectable colonic HIV RNA tended to be at earlier stages of AHI.

49 Identification and Characterization of Individual HIV-Infected CD4 T Cells Ex Vivo

Joseph Casazza[1]; Irene Primmer[1]; David Ambrozak[1]; Constantinos Petrovas[1]; Sara Ferrando-Martinez[1]; Perla Del Río-Estrada[2]; Gustavo Reyes-Terán[2]; Ezequiel Ruiz-Mateos[3]; John Mascola[1]; Richard A. Koup[1]

[1]Vaccine Research Center, NIAID, NIH, Bethesda, MD, US; [2]Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico; [3]HU Virgen del Rocio/IBIS, Sevilla, Spain

Background: Identification of live HIV-infected CD4 cells would allow the characterization of these cells by flow cytometry and single cell transcriptomic analysis.

Methods: bnAbs were screened for their ability to identify individual BaL-infected primary CD4 T cells as identified by P24 intracellular staining and transcription of Gag, and D1A3 (Tat-associated) and D1A4b (Rev-associated) spliced HIV RNA. CD4 mimic, V1V2 and the V3 glycan bnAbs were found that stained BaL-infected cells. bnAbs used for *ex vivo* studies were selected based on breadth of neutralization of B clade virus, and sensitivity and intensity of staining of HIV-infected CD4 T cells. Live $CD3^+CD45RO^+CD8^-CD14^-CD19^-TCR\delta\gamma^-$ CD4 dim and null cells prepared from lymph nodes were stained for expression of PD-1, CD57, CXCR4, CXCR5, CD27 and PGT121 and then bulk sorted into $PD\text{-}1^{++}$; $PD\text{-}1^-CD57^-$; and $PD\text{-}1^-CD57^+$ populations. Individual $PD1^+$ cells were index sorted into individual wells, RNA was extracted, purified, and Gag, and Rev- and Tat-associated RNA copy numbers determined by RT PCR. Measureable Tat- and Rev-associated HIV RNA were assumed to represent active transcription of HIV proviral DNA.

Results: The highest frequency of CD4 T cells transcribing proviral DNA was found in the $PD\text{-}1^+$, CD4 dim and null population. $PD\text{-}1^+$ cells were index sorted and Gag, Tat- and Rev-associated HIV RNAs measured. Ninety-one of 599 (15%) cells sorted from lymph nodes from six untreated, HIV-infected individuals, were actively transcribing HIV RNA. Eighty-five percent of the cells transcribing Tat- and Rev-associated RNA also contained measurable Gag RNA. Staining of HIV envelope by PGT121 was significantly associated with proviral DNA transcription ($P<0.0001$). Median percentage of $PGT121^+$ CD4 dim and null T cells actively transcribing virus was 41 (range, 12-64)% compared to 17(3-22)% in $PGT121^-$ cells. PGT121 staining was strongly associated with downregulation of CD4 ($P<0.0001$). A higher percentage of $CXCR5^+PD1^+$ cells actively transcribed proviral DNA than did $CXCR5^-PD\text{-}1^+$ cells ($P<0.0001$). A lesser proportion of $CD57^+$ CD4 T cells, a marker of germinal center cells, actively transcribed proviral DNA than did $CD57^-$ CD4 T cells ($P<0.05$).

Conclusions: Most CD4 T cells transcribing proviral DNA are Tfh cells. Viral transcription occurs both inside and outside of the germinal center in B cell follicles and is identifiable by bnAbs. bnAbs may be a means of targeting HIV-infected CD4 T cells in lymph nodes.

50 Efficacy of HIV-1 Monoclonal Antibody Immunotherapy in Acute SHIV-Infected Macaques

Diane L. Bolton[1]; Amarendra Pegu[2]; Keyun Wang[2]; Kathleen McGinnis[2]; Kathryn Foulds[2]; Srinivas Rao[2]; Merlin L. Robb[1]; Nelson L. Michael[1]; John Mascola[2]; Richard A. Koup[2]

[1]US Military HIV Research Program, Silver Spring, MD, US; [2]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

Background: Highly potent broadly neutralizing HIV-1 antibodies (bNAb) can suppress viremia in both humanized mouse and macaque models of HIV-1 infection. However, the therapeutic potential of these antibodies during early acute infection (e.g. Fiebig I-III) is unknown. Recent clinical evidence indicates that antiretroviral therapy (ART) administered during this period suppresses both viremia and seeding of the viral reservoir. Here we test the ability of bNAb regimens to control acute simian-human immunodeficiency virus (SHIV) replication in rhesus macaques and compare efficacy to ART.

Methods: Rhesus macaques were infected with SHIV-SF162P3 followed by administration 10 days later of either 1) daily triple drug ART; 2) a single dose of Env CD4-binding site specific bNAb, VRC01; 3) a single dose of a combination of a more potent clonal relative of VRC01 (VRC07-523) and a V1/V2 glycan-dependent bNAb (PGT121); or 4) no treatment. Daily ART was initiated 11 days after bNAb. Plasma viremia and cell-associated viral load were measured to assess efficacy.

Results: A single infusion of VRC01 on day 10 reduced viremia by ~ 1 log10 over the next 10 days. The combination of VRC07 and PGT121 had a greater effect of between 2 and 3 log10 that was similar to treatment with ART. Following peak viremia, control was better sustained by the dual bNAb and ART regimens than the VRC01 regimen. Plasma bNAb concentrations exceeded IC80 values for at least 7 days in all animals. Proviral DNA in lymph node was also diminished after treatment with ART or dual bNAb, both effecting a ~1 log decline in SHIV copies per $CD4^+$ T cell. Decreased viral replication by these regimens was further evidenced by dampened cellular and humoral immune responses to viral antigens. Greater efficacy of VRC07-523 / PGT121 relative to VRC01 is consistent with more potent neutralization activity of these bNAbs against the SHIV-SF162P3 challenge virus.

Conclusions: Our findings demonstrate that potent neutralizing HIV-1-specific antibodies are at least as effective as ART at controlling acute virus replication. Moreover, bNAb immunotherapy may offer an advantage over ART in its ability to further reduce the proviral DNA burden. These data support future therapeutic clinical trials that investigate VRC01, and eventually other antibodies, as an alternative to or in conjunction with ART to treat Fiebig I-III HIV-1 infection.

51 HIV-1 Infections With Multiple Founders Are Associated With Higher Viral Loads

Holly Janes[1]; Sodsai Tovanabutra[2]; Joshua Herbeck[3]; Supachai Rerks-Ngarm[4]; Merlin L. Robb[2]; Nelson L. Michael[2]; Peter Gilbert[1]; Jerome H. Kim[2]; **Morgane Rolland**[2]
The Step/HVTN502 and RV144 study teams

[1]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [2]US Military HIV Research Program, Silver Spring, MD, US; [3]University of Washington, Seattle, WA, US; [4]Thai Ministry of Public Health, Bangkok, Thailand

Background: A single HIV-1 genetic variant establishes infection in most subjects, including breakthrough infections in the Step/HVTN-502 and RV144 vaccine efficacy trials. We sought to evaluate whether characteristics of the founder viral populations could influence clinical outcomes in the infected participants, specifically whether subjects infected with multiple founder variants would exhibit higher viral loads or lower CD4+ T cell counts.

Methods: HIV-1 breakthrough sequences obtained by single genome amplification from plasma samples collected at diagnosis, and follow up clinical data were available from 63 Step/HVTN502 (MSM infected with HIV-1 subtype B) and 100 RV144 (heterosexuals infected with HIV-1 CRF01_AE) participants. Linear regression models were used to relate qualitative (homogeneous/heterogeneous infection) and quantitative (*env* diversity measures) viral predictors to clinical post-infection endpoints.

Results: Based on data collected up to 1 year post HIV-1 diagnosis, we found that subjects who had been infected with multiple founder viruses had significantly higher mean viral loads (0.37 $\log_{10}$ higher, $p = 0.007$ in Step and 0.29 $\log_{10}$ higher, $p = 0.024$ in RV144). Higher *env* diversity in the founder population was also associated with higher mean viral load (0.59 $\log_{10}$ higher per 10-fold increase in diversity, $p \leq 0.001$ in Step and 0.45 $\log_{10}$ higher per 10-fold increase in diversity, $p = 0.011$ in RV144). Moreover, in the RV144 cohort, subjects with more diverse HIV-1 founder populations had significantly lower CD4 T cell counts over time (heterogeneity predictor: $p = 0.020$, *env* diversity predictor: $p = 0.028$).

Conclusions: We showed that measures of increased HIV-1 diversity in early HIV-1 infection, both qualitative and quantitative, were associated with markers of poorer clinical outcomes. These results illustrate how consequential the first steps of HIV-1 infection are for clinical disease progression and suggest that limiting the number of viral variants establishing HIV-1 infection may be an important goal for HIV-1 preventive and post-infection disease attenuation strategies.

The views expressed are those of the authors and should not be construed to represent the positions of the US Army or the Department of Defense.

52 Post-Treatment Controllers Have Particular NK Cells With High Anti-HIV Capacity: VISCONTI Study

Daniel Scott-Algara[1]; Céline Didier[1]; Vincent Arnold[1]; Jean-Saville Cummings[1]; Faroudy Boufassa[2]; Olivier Lambotte[5]; Laurent Hocqueloux[4]; Asier Sáez-Cirión[1]; Christine Rouzioux[3]

[1]Institut Pasteur, Paris, France; [2]CESP U1018 Inserm, Le Kremlin-Bicêtre, France; [3]Laboratoire de Virologie, EA 3620–Université Paris Descartes Hôpital Necker, Paris, France; [4]Service des Maladies Infectieuses et Tropicales CHR d'Orléans–La Source, Orleans, France; [5]Hôpital Bicêtre, Le Kremilin-Bicêtre, France

Background: The association of T-cells with the control of HIV infection has been well documented. In addition, several studies pointed out the role on innate immune responses in the resistance or delay to HIV disease progression. The recent description (VISCONTI study) of a group of patients, so-called post-treatment controllers (PTCs), who remains with undetectable viral load after treatment interruption despite poor CD8+T cell responses, led us to study NK cells and their relationship to HIV control.

Methods: 14 patients enrolled in the French ANRS VISCONTI cohort were studied. PTCs' results were compared to those of Viremic patients, (VIR), natural HIV controllers (HIC), patients on ARV since acute infection (ARV) and normal blood donors (controls). All phenotypic studies were done on fresh whole blood. CD107a expression on NK cells and the ICS-based assay were done on PBMC after stimulation. NK cells were tested for their capacity to inhibit HIV infection (measured by intracellular or supernatant p24) in autologous CD4 T cells. Results obtained were compared using Wilcoxon rank sum test or by the Fisher exact test

Results: Visconti patients showed significantly higher expression of CD158a, CD158b (KIR2DL2/DL3), PTC showed significantly higher expression of CD158a, CD158b (KIR2DL2/DL3), CD158b/DX9 (KIR3DL1/3DS1) and NKG2A receptors ($p<0.002$, $p<0.001$, $p<0.0.01$, $p<0.001$, respectively) with lower expression of CD160 and NKp46 ($p<0.001$, $p<0.03$, respectively) receptors compared to others groups. Activation of NK cells from PTC and ARV, measured by CD69 marker, was similar to normal donors but lower than in HIC ($p<0.006$) or VIR patients ($p<0.001$). Functional studies when NK cells were stimulated by K562 cell line showed normal levels of degranulation (CD107a marker) but higher IFN-γ production for PTC than for other groups ($p<0.01$). NK cells from PTCs, but not from other individuals ($p<0.001$), were able to reduce p24 levels when co-cultured with in vitro-infected autologous CD4 T cells.

Conclusions: NK cells from PTC had a different NK cell repertoire and higher potential to produce IFN-γ compared to HIC, Viremic patients or normal donors, but similar to those treated since primary infection. More importantly, PTC NK cells showed high capacity to control in vitro HIV infection on autologous CD4 T cells. Our results suggest that preserving NK cell phenotype and function during acute infection is important to control HIV and identify NK cells as possible important agents in the durable remission of PTC.

53 Antiretroviral Therapy Preserves Polyfunctional HIV-1–Specific CD8 T Cells With Stem-Cell–Like Properties

Selena Vigano[1]; Jordi J. Negron[1]; Eric S. Rosenberg[2]; Bruce D. Walker[1]; Mathias Lichterfeld[2]; Xu G. Yu[1]

[1]The Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

Background: CD8 stem-cell like memory T cells (T_{SCM} cells) have been recently identified in humans, mice and non-human primates, and seem to represent the most immature memory CD8 T cell population with potent abilities to proliferate and repopulate the memory T cell pool. The presence and the function of CD8 T_{SCM} cells in HIV-1 positive individuals are unknown.

Methods: CD8 T_{SCM} cells were analyzed in 61 HIV-1-positive patients (31 with HAART-suppressed HIV-1 infection, 14 with untreated progressive HIV-1 infection, and 16 untreated HIV-1 controllers (viremia < 1000 RNA copies/ml). Phenotype and function of CD8 T_{SCM} cells were assessed by flow cytometry; virus-specific CD8 T cell populations (n=90 HIV-1-specific responses, n=24 CMV/EBV/Flu-specific responses) were identified by MHC class I multimer staining or intracellular cytokine staining. 12 HIV-1 negative study subjects were analyzed as controls.

Results: Levels of T_{SCM} in total CD8 T cells were significantly decreased in untreated HIV-1-infected patients ($p<0.007$), but not different between HAART-treated HIV-1 patients and HIIV-1-negative subjects. Among all HIV-1 patients, total and HIV-1-specific CD8 T_{SCM} cells were most frequent in HAART-treated patients ($p<0.0001$). CD8 T_{SCM} cell frequency was directly associated with years of treatment ($p<0.0001$, r=0.66) and inversely associated with immune activation ($p=0.007$, r=-0.3) and apoptosis ($p=0.03$, r=-0.27) levels. Moreover, HIV-1-specific CD8 T_{SCM} cells from HAART-treated patients showed the highest degree of polyfunctionality in comparison to the other groups of patients ($p<0.005$).

Conclusions: Polyfunctional HIV-1-specific CD8 T_{SCM} cells are able to persist long-term and show a relative accumulation during antiretroviral therapy when viral antigen is pharmacologically suppressed. Due to their apparent antigen-independent persistence in HAART-treated patients, these cells may play an important role in targeting the reservoir of HIV-1-infected cells after pharmacological reversion of viral latency.

54LB In Vitro Replication and Interferon-Alpha Resistance of Transmitted HIV-1 Variants

Zachary Ende[1]; Martin Deymier[1]; Angharad Fenton-May[2]; Daniel T. Claiborne[1]; William Kilembe[3]; Susan Allen[1]; Persephone Borrow[2]; Eric Hunter[1]

[1]Emory University, Atlanta, GA, US; [2]Oxford University, Oxfordshire, United Kingdom; [3]Zambia Emory HIV Research Project, Lusaka, Zambia

Background: Despite the diverse quasispecies of HIV-1 in the transmitting partner, a bottleneck occurs during transmission whereby, in general, a single genetic variant from that quasispecies establishes infection in the new host. The current working model explaining the transmission bottleneck suggests that transmitted/founder (TF) variants have a higher *in vivo* fitness and are preferentially resistant to the innate antiviral effects of interferon alpha (IFNα), enabling escape from the early innate immune response. However, variants derived from HIV-1 transmission pairs with the full complement of HIV proteins have yet to be tested for IFNα resistance or *in vitro* replication. In this study, we assess replication and IFNα resistance of infectious molecular clones derived from both partners from six transmission pairs to compare the TF to non-transmitted (NT) variants that were present near the time of transmission.

Methods: Using a novel cloning strategy, we generated 44 HIV-1 subtype-C full-length infectious molecular clones (6 TF & 38 non-transmitted (NT) variants) from plasma of 6 linked transmission pairs near the time of transmission from the Zambia-Emory HIV Research Project (ZEHRP). The NT variants were selected to represent the sequence diversity of the transmitting partner. We measured virus growth in stimulated PBMC and compared the levels of replication in the presence and absence of IFNα to determine IFNα resistance of the TF and NT variants.

Results: We found no evidence of selection for IFNα resistance during heterosexual transmission ($p=0.7813$), when comparing the TF to matched NT variants. We also did not observe selection for TF varaints with higher *in vitro* replicative capacity than the median of the matched NT variants ($p=0.7118$). Notably, the *in vitro* replicative capacity of each variant correlated with the ability to replicate in the face of IFNα ($p<0.0001$) and replicative capacity correlated negatively with IFNα resistance ($p<0.0001$).

Conclusions: Our results emphasize the importance of comparing TF variants to NT controls near the time of transmission and suggest that IFNα resistance and *in vitro* replicative capacity are not necessarily selected for during transmission of subtype C HIV-1 variants. Further characterization of TF variants is necessary to fully understand the viral properties selected for during the HIV-1 transmission bottleneck and to optimize protection through vaccines or other prevention modalities.

55LB HVTN505 Breakthrough Sequences Show HIV Vaccine-Associated Differences in Env-gp120

Morgane Rolland[1]; Allan deCamp[2]; Breana M. Hall[3]; Sodsai Tovanabutra[1]; Mario Roederer[4]; Scott M. Hammer[5]; Magdalena E. Sobieszczyk[5]; Peter B. Gilbert[2]; Jerome H. Kim[6]; James Mullins[3]
The HVTN505 Sieve Analysis Group

[1]US Military HIV Research Program; Henry M. Jackson Foundation for the Advancement of Military Medicine Inc, Silver Spring, MD, US; [2]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [3]University of Washington, Seattle, WA, US; [4]Vaccine Research Center, Bethesda, MD, US; [5]Columbia University, New York, NY, US; [6]US Military HIV Research Program, Silver Spring, MD, US

Background: The HVTN505 HIV vaccine study enrolled 2,504 US participants in a phase IIb test-of-concept efficacy trial of a DNA/rAd5 vaccine expressing Gag/Pol/Nef from subtype B and Env proteins from subtypes A/B/C. Although the vaccine showed no efficacy with respect to HIV acquisition or post-infection viral load (Hammer, NEJM, 2013), we analyzed breakthrough HIV isolates to evaluate potential sieve effects.

Methods: Sequencing was performed following PCR amplification of near full-length single HIV genomes derived from plasma specimens at HIV diagnosis. Phylogenetic and statistical analysis methods assessed individual genes, k-mers, and amino acid (AA) sites to compare breakthrough sequences from vaccine and placebo recipients, with multiplicity adjustment procedures (20% false discovery rate).

Results: We characterized 480 HIV genomes from 27 vaccine and 20 placebo recipients. All infections were with subtype B. Infections were established by multiple founder variants in 5 of 26 vaccine recipients (19%) and in 8 of 20 placebo recipients (40%) (Fisher's exact test, p= 0.19). Two vaccine recipients were infected by two phylogenetically-unrelated viruses (*env* diversity= 8.9% vs 0.3% for other subjects). Intra-host diversity was significantly lower in vaccine than placebo recipients for Gag, Pol, Env-gp120 and Vif proteins ($p \leq 0.04$, $q \leq 0.09$).

The distance between founder and vaccine sequences was measured for each participant and compared across treatment groups. While differences in other proteins were not significant, Env-gp120 sequences from vaccine recipients were significantly more distant from the subtype B vaccine insert than sequences from placebo recipients (median = 0.30 vs 0.29; Mann-Whitney test, p= 0.01, q= 0.12).

Vaccine/placebo AA differences in Env-gp120 were identified at six 9-mers starting at HXB2 positions 28, 86, 193, 365, 427, and 467, and at site 133 ($p < 0.005$, $q < 0.2$). Mapping of the 9-mer starting at AA193 on a trimer structure showed these residues in contact with the tip of the V3 loop of another monomer, thus possibly affecting the binding of V3-specific antibodies (Fig.1) – an interesting finding as the HVTN505 vaccine regimen elicited strong anti-V3 responses.

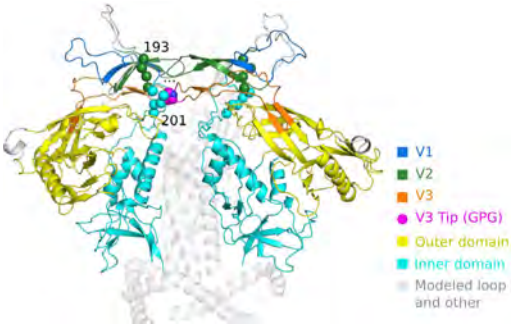


Figure 1. Env-gp120 residues corresponding to the 9-mer starting at HXB2 position 193 that distinguished the vaccine and placebo groups are figured with circles on the BG505. SOSIP structure (PDB ID: 4NCO). The start and end residues of the 9-mer (AA193 and 201) are numbered on the monomer on the left, the residues are colored in green and turquoise with a mirror image on another monomer. At the tip of the V3 loop, GPG is in magenta, with the 5 atoms in the proline's ring shown as spheres (the N atom being a blue sphere, carbon atoms in magenta).

Conclusions: Our results suggest an HVTN505 vaccine-driven sieve effect against Env-gp120. Analysis of breakthrough HIV isolates in vaccine efficacy trials is important to assess whether a vaccine elicited a selective pressure *in vivo* and to identify which responses are associated with efficacy and which are not.

Themed Discussion Abstracts

258 PCR-Free Full Genome Characterization of Diverse HIV-1 Strains by Nextgen Sequencing

Viswanath Ragupathy[1]; Feng Gao[2]; Ana Sanchez[2]; Marco Schito[3]; Thomas Denny[2]; Michael Busch[4]; Jiangqin Zhao[1]; Christelle Mbondji[1]; SaiVikram Vemula[1]; Indira Hewlett[1]

[1]US Food and Drug Administration, Silver Spring, MD, US; [2]Duke Human Vaccine Institute and Departments of Medicine, Duke University Medical Center, Durham, NC, US; [3]Henry Jackson Foundation, DAIDS, NIAID, Bethesda, MD, US; [4]Blood Systems Research Institute/University of California San Francisco, San Francisco, CA, US

Background: HIV-1 genotyping is an important tool for clinical and epidemiological studies. High level of genetic variation, recombination and mutations pose difficulty in successful PCR amplification of HIV-1 genomes. In addition, new emerging subtypes may not be detected with standard PCR primers. Here, we report a novel PCR-free multiplex method for characterization of full length HIV-1 genomes (~9.7kb) using the Nextgen RNA Seq approach.

Methods: A total of 27 diverse HIV-1 strains representing subtypes A-G, CRFs, URFs and Group O were obtained from the Global HIV-1 diversity panel that was assembled at the Duke EQAPOL. Viral RNA was extracted, reverse transcribed as described in the Illumina Truseq RNA Kit and sequenced using the MiSeq platform. Sequence reads were quality filtered and reference mapped using CLC genomic work bench software v6.0.4. Consensus sequences were generated for each virus and used for phylogenetic tree analysis using the neighbor-joining method based on the Kimura two-parameter substitution model and recombination patterns were determined using Simplot. Drug resistance was inferred from the Stanford HIV drug resistance program, and co-receptor usage was determined using the Geno2Pheno (g2p) 5-10% FPR.

Results: The multiplex RNA sequencing approach yielded >10000x coverage for each of the viral genomes. Pools of viral isolates were de-multiplexed and discriminated using bio-informatics. After filtering reads specific for HIV-1, each position in the viral genome had >1000x coverage. This approach enabled reconstruction of whole genome HIV-1 haplotypes accurately including flanking LTRs. Analysis of full HIV-1 genome sequences using Simplot correctly identified 15 pure subtypes, one Group O virus, and recombination patterns of 8 CRFs and 3 URFs. All these HIV subtypes identified were comparable to Sanger sequencing. In addition, this approach revealed NNRTI, integrase and protease drug-specific minor variants and drug resistance mutations with >1000x coverage. The g2p analysis predicted 89% of isolates as being R5 tropic, and the remaining were identified as X4 tropic.

Conclusions: We have developed a reliable, PCR-free and multiplexing approach to characterize whole HIV-1 genome sequences. This novel PCR-free method can be used for characterization of new, emerging unknown subtypes or recombinants and to reduce PCR-derived sequence errors. The multiplexing approach makes this NGS method more cost-effective and less labor-intensive than conventional methods.

257 Pan-HIV Next-Gen Sequencing Strategy for Viral Surveillance

Michael G. Berg[1]; Julie Yamaguchi[1]; Elodie Alessandri-Gradt[2]; Jean-Christophe Plantier[2]; Catherine Brennan[1]
[1]Abbott Laboratories, Abbott Park, IL, US; [2]Virology Unit, National Reference for HIV, Rouen, France

Background: The complexity of HIV strains has increased significantly due to natural evolution and inter-subtype recombination; recombination is now a worldwide problem. Thus, complete genome sequencing is essential to monitor HIV diversity accurately within populations. Next-generation sequencing (NGS) has the potential to revolutionize strategies for HIV surveillance. We have developed a universal method that permits full genome sequencing of all HIV-1 groups (M, N, O, and P) and HIV-2.

Methods: Reverse transcription primers, designed in conserved regions of HIV and spaced at 1.5-2kb intervals, fuse viral sequences to a common adaptor (SMART) sequence. This same adaptor is added to the 3' end of the cDNA to permit PCR amplification of libraries, which are then tagmented with Nextera XT for multiplexing and sequencing on an Illumina MiSeq. HIV sequences are extracted and assembled in CLC-Bio software (Qiagen) and classified by phylogenetic analysis using PHYLIP and SIMPLOT.

Results: Broad application of the approach was demonstrated using a panel of virus isolates (n=47) derived from cell culture that included 27 group M (different subtypes and CRFs), 16 O, 2 N, 1 P, and 1 HIV-2. In a single run multiplexing 23 libraries, 100% genome coverage was obtained for each at a median depth of 2100X, with HIV reads comprising 9.4% (median) of the total. A Cameroonian HIV-1 non-subtype B specimen was used to optimize the protocol for plasma. An NGS run of 8 high titer (>5.0_{log} copies/ml) clinical specimens, infected with diverse group M subtypes, yielded 96-100% coverage for each at a median 433X depth. Method sensitivity, demonstrated by serial dilution, showed that >50% of a genome could be obtained from a clinical specimen with a viral load ≥3.8_{log} copies/ml (100 RNA copies input). Due to inherent variability in sample background, coverage varied widely among specimens with viral loads <4.5_{log}. Nevertheless, sufficient sequence was obtained for strain classification. From the 55 novel full-length HIV sequences determined in this study, 5 are unique recombinants.

Conclusions: The HIV-SMART approach harnesses the specificity of HIV-directed priming without *a priori* knowledge of the viral strain present. This technology provides an unparalleled opportunity to identify diverse HIV strains in patient specimens and to determine phylogenetic classification based on the entire viral genome, illustrating the utility of NGS for viral surveillance.

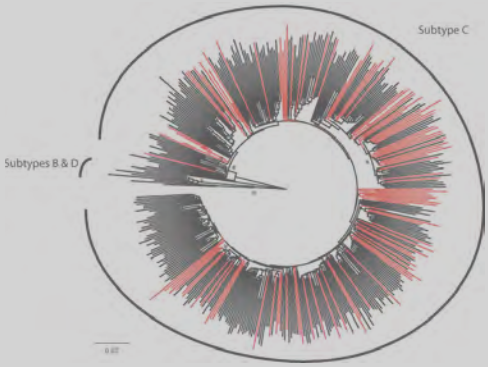
256 Near Full Length HIV-1 Sequencing to Understand HIV Phylodynamics in Africa in Real Time

Siva Danaviah; Justen Manasa; Eduan Wilkinson; Sureshnee Pillay; Zandile Sibisi; Sthembiso Msweli; Deenan Pillay; **Tulio de Oliveira**
University of KwaZulu-Natal, Durban, South Africa

Background: HIV transmission continues in Africa at alarming rates despite biological and behavioural interventions. Understanding the drivers of HIV transmission and evolution and translating the results into effective interventions is a key component of halting the epidemic. Recent technological advancement in complete genome sequencing has expanded the breadth and speed of genomic analyses currently possible. We have constructed a high-throughput genomics and bioinformatics pipeline that has successfully generated high quality complete HIV genomes in a hyper-endemic region of South Africa (SA), through the PANGEA_HIV Consortium

Methods: HIV RNA was extracted from plasma from patients failing antiretroviral therapy, within the Africa Centre (AC) research area and 4 overlapping regions spanning the 9.7kb complete HIV genome were amplified in a one-step RT-PCR strategy optimised for subtype C virus. Pooled amplicons were sequenced on an Illumina MiSeq. Fragments were quality controlled with SMALT software and assembled using two independent strategies (de novo and mapping to reference) in Geneious. Resulting consensus sequences were aligned against published HIV complete genomes from South Africa (n=300). Bayesian and maximum likelihood trees with branch support were reconstructed in PhyML and MrBayes.

Results: Amplification success rate of complete genomes, on samples with viral loads >10,000 c/ml was 85%. Near complete HIV genomes were generated for 117/117 samples sequenced thus far, with all nine open reading frames, the U5 / partial R region of the 5' LTR and partial U3 of the 3' LTR represented. Coverage of the HIV genome averaged 99.9% with a mean depth of coverage of 15 539 times (range = 21-48 767 times). Phylogenetic reconstruction confirmed that the AC strains were all HIV-1 subtype C where 36/117 sequences clustered with other complete genomes from SA. The discrete AC clusters (n=22) suggested multiple independent introductions of subtype C into the surveillance area and onward transmission within the population.



Maximum likelihood tree of 117 Africa Centre near full length HIV-1 complete genomes and 300 HIV-1 C genomes from South Africa. The tree is rooted on reference strains of subtypes B & D, branch support (bootstrap > 90) are marked with an *.

Conclusions: This is the first report, to the best of our knowledge, of a high-throughput complete HIV genome sequencing and analysis pipeline in Africa. The genetic diversity of HIV variants in this population is high and is mediated primarily by multiple introductions of HIV. Interventions therefore must be cognizant of the dynamics that drive these independent introductions in order to impact on going HIV transmission.

254 Present Applications of a High-Throughput, Single Measure HIV Genomic Incidence Assay

Sung Yong Park[1]; Tanzy Love[2]; Nolan Goeken[1]; Robert Bolan[3]; Alan S Perelson[4]; Michael Dube[1]; **Ha Youn Lee**[1]
[1]Keck School of Medicine at University of Southern California, Los Angeles, CA, US; [2]University of Rochester School of Medicine and Dentistry, Rochester, CA, US; [3]Los Angeles Gay and Lesbian Center, Los Angeles, CA, US; [4]Los Alamos National Laboratory, Los Alamos, CA, US

Background: Annual HIV incidence is the primary assessor for monitoring the epidemic's rise and decline. In pursuit of an accurate assay, we have proposed a genomic incidence assay utilizing fingerprints harbored in the HIV sequence population, which showed over 95% accuracy among 182 incident and 43 chronic samples. Still, two major hurdles must

be overcome before routine use in cross-sectional settings: 1) streamlining the cost and workflow, 2) ensuring proper classification between multiple-founder recent infections and chronic infections.

Methods: For enhancing the cost efficiency of the sequence-based assay, we developed a high-throughput next-generation sequencing platform; a signal-masking bioinformatics pipeline was devised to analyze 18,434 envelope gene segments (HXB2 7212-7601) obtained from 12 incident and 24 chronic patients. To give the assay power to appropriately discriminate multiple-founder recent infections from chronic infections, we formulated a mathematical model which posits the intersequence nucleotide base difference distribution of each subject's sequence sample as a function of infection duration and the number of founder sequences. This model was tested by analyzing HIV subtype B and C samples from 40 incident subjects with multiple founder viruses.

Results: First, the cost-effective pyrosequencing platform correctly classified all 12 incident subjects (100% sensitivity) and 23 out of 24 chronic subjects (96% specificity). Our signal-masking bioinformatics pipeline yielded a process error rate of 5.8×10^{-4} per base. Sampling simulations showed that the biomarkers were tolerant of the two factors most likely to affect the accuracy: sequencing errors and template resampling. Second, a quantitative guideline for segregating viral lineages was provided by our mathematical model, enabling us to assess when each subject was infected. The infection periods obtained from our model estimates and from Fiebig laboratory staging showed a statistically significant linear relationship ($p<0.0005$), correctly identifying all 40 individuals with incident infections.

Conclusions: The high-throughput platform permits the assay to be cost-effective, and when it is combined with our mathematical model, we can obtain recency signatures from the complex gene pool that arises from multiple founder viruses. Our sequence-based approach marks significant progress towards accurate determination of HIV incidence from genomic readouts measured from cross-sectional samples from a single blood draw.

255 A Comprehensive Analysis of Primer IDs to Study Heterogenous HIV-1 Populations

David Seifert[1]; Armin Töpfer[1]; Francesca Di Giallonardo[2]; Stefan Schmutz[2]; Huldrych F. Günthard[2]; Volker Roth[3]; Niko Beerenwinkel[1]; Karin J. Metzner[2]

[1]ETH Zurich, Basel, Switzerland; [2]University Hospital Zurich, Zurich, Switzerland; [3]University of Basel, Basel, Switzerland

Background: Haplotyping of HIV-1 populations is an essential step to better understand the evolutionary dynamics of the virus. With the advent of next-generation sequencing (NGS), haplotyping of viral populations has become feasible. Since HIV-1 is highly heterogeneous, several statistical methods have been devised to deal with error-prone NGS data, however, they often do not capture the population correctly. In order to correct for errors, the use of PrimerIDs (primer identifiers) has been proposed. Here, we used PrimerIDs to systematically estimate different enzymatic error rates and to comprehensively study the feasibility of PrimerIDs.

Methods: Plasmids containing full-length genomes of 5 HIV-1 clones were separately amplified in bacteria and then transfected into 293T cells. Generated infectious HIV-1 particles were pooled, DNase treated, and a fragment of the *pol* gene was reverse transcribed with SuperScript III reverse transcriptase (RT) and primers containing random 10-mers. Reverse transcription was performed in six independent replicates. Subsequently, nested PCR was performed using Platinum Taq DNA Polymerase followed by adapter ligation and sequencing with Illumina MiSeq.

Results: From an average number of 1.1 million reads, we called consensus sequences for PrimerIDs, each supported by at least 10 sequencing reads, to yield on average 11,000 consensus sequences per replicate. From these consensus sequences, we could call all mutant bases from the five reference viruses. We estimated a RT error rate of 6.23e-4 (95% CI: [6.13e-4, 6.32e-4]). We inferred the recombination rate of the RT to be 3.44e-5 (95% CI: [2.26e-5, 4.92e-5]). The PCR substitution rate of 1.18e-4 (95% CI: [1.14e-4, 1.22e-4]) was determined from those mutants having arisen in the first cycle of the PCR. We calculated the total number of transcribed RNAs to be on the order of 60,000 from the observed collision rate of 2%. We observed no sequence-specific bias in PrimerID frequencies, the same RT efficiencies as compared to commonly used short, specific RT primers, and no effects of primerIDs on the estimated distribution of the five viruses in the mix.

Conclusions: PrimerIDs allow for determining error rates in RT-PCR-NGS protocols and are applicable to study HIV-1 heterogeneity when attention is paid to collision rates. Given these advantages, the protocol is still labor- and cost-intensive and does not significantly improve on the variance of frequency estimates.

593 Analysis of Resistance Haplotypes Using Primer IDs and Next Gen Sequencing of HIV RNA

Valerie F. Boltz[1]; Jason Rausch[1]; Wei Shao[2]; Charles Coomer[1]; John W. Mellors[3]; Mary Kearney[1]; John M. Coffin[4]

[1]National Institutes of Health (NIH), Frederick, MD, US; [2]Leidos, Frederick, MD, US; [3]University of Pittsburgh, Pittsburgh, PA, US; [4]Tufts University, Boston, MA, US

Background: Targeted sequencing technologies using primer IDs can result in more accurate representations of HIV-1 populations but PCR bias and recombination have hampered progress. Here we describe a new method for library construction that produces a larger number of tagged consensus sequences, increases sensitivity of haplotype determination, and reveals the sources of recombination.

Methods: Each molecule of cDNA from mixtures of varying percentages of wild-type and mutant HIV-1 *pol* transcripts containing 14 drug resistance mutations was tagged uniquely using a gene-specific primer with primer IDs. cDNAs were then PCR amplified using two methods: (1) 90mer primers containing required MiSeq sequences; (2) 22mer primers containing uracil followed by digestion, cleavage and ligation to linkers containing MiSeq sequences. DNA was sequenced using paired-end MiSeq Illumina technology and consensus sequences were derived from a super-majority (≥80% consensus) for each unique ID. Consensus sequences were analyzed for PCR bias, errors, recombination, and sensitivity for detecting haplotypes.

Results: Of the total cDNA molecules used as template, amplified cDNA with unique tags ranged from 3-19% for method 1 and from 15-52% for method 2. The average error rates for method 1 and 2 were $9.3\text{x}10^{-5}$ and $1.4\text{x}10^{-4}$, respectively, both comparable to RT error rates. The PCR recombination rate for method 1 was 0.16% but only 0.01% for method 2. Method 1 was able to detect drug resistance mutations down to 0.01% and method 2 down to 0.001%. The sensitivity of haplotype detection was better for method 2: for samples containing 10% or 1% mutant, method 1 never detected linkage of all 14 mutations, whereas method 2 detected all 14 33-35% of the time. Method 2 always detected linkage of the 8 mutations nearest the 3′ end of the amplicon suggesting that PCR recombination is due to incomplete cDNA synthesis.

Conclusions: A linker ligation method of amplifying tagged cDNA reduced both PCR bias and recombination rate compared to standard methods, and was superior at detecting haplotypes within 200bp of the 3′ end of the template. However, it correctly detected linkage across the entire 570bp amplicon in only 1/3 of sequences, suggesting that cDNA synthesis is typically incomplete leading to PCR recombination and thus limiting sensitivity for detection of linked mutations. Improved methods are needed for cDNA synthesis to increase the reliability of haplotype determination for HIV-1 populations.

300 Effect of CMV and HIV Replication on T-Cell Exhaustion and Senescence During ART

Jennifer M. Dan[1]; Marta Massanella[1]; David M. Smith[1]; Eric S. Daar[2]; Michael P. Dube[3]; Richard Haubrich[1]; Sheldon Morris[1]; Sara Gianella Weibel[1]

[1]University of California San Diego, La Jolla, CA, US; [2]Harbor–University of California Los Angeles Medical Center, Torrance, CA, US; [3]University of Southern California Keck School of Medicine, Los Angeles, CA, US

Background: HIV-infected men who have sex with men (MSM) are nearly universally infected with CMV, and both viruses are associated with T-cell dysfunction and inflammation-related morbidities. The effect of asymptomatic CMV replication and persistent HIV transcription during suppressive ART on markers of T cell exhaustion and senescence is poorly defined.

Methods: Paired seminal and blood samples from 45 asymptomatic chronically HIV-infected CMV-seropositive MSM on long term ART and with HIV RNA levels in blood plasma <50 copies/ml were studied. Levels of CMV DNA in semen and blood were measured by RT-PCR, and cell-associated HIV DNA and RNA transcripts (unspliced) were measured in PBMC by droplet digital PCR. Markers of T cell exhaustion (PD-1) and senescence (CD57) were measured in PBMC by flow cytometry for CD4 and CD8 T cells and subsets (naïve [$CD45RA^+CD27^+CD28^+$], central memory [$CD45RA^-CD27^+CD28^+$], effectors [$CD4^+CD45RA^{-/+}CD27^-CD28^+$ or $CD8^+CD45RA^{-/+}CD27^+CD28^-$] and terminally differentiated [$CD45RA^{+/-}CD27^-CD28^-$]). Associations between immunological markers and asymptomatic CMV and HIV replication, HIV DNA, CMV IgG, age, current and nadir CD4 and time on ART were determined using univariate and multivariate analysis.

Results: CMV DNA was detected in 42% of seminal samples and 20% of PBMC. Detectable CMV DNA in semen but not blood was associated with increased PD-1 expression on circulating CD4 T cells compared to no CMV (P=0.01), particularly in the effector and terminally differentiated subsets (P<0.05). Similarly, higher levels of cellular HIV RNA (but not HIV DNA) were positively associated with greater PD-1 expression on total CD4 and central memory blood subset (P<0.01). There was no association between CMV DNA (blood and semen) or cellular HIV RNA with CD8 exhaustion or senescence or with markers of CD4 senescence. In multivariate analysis, detection of seminal CMV and higher cellular HIV RNA remained associated with increased PD-1 expression on total CD4 T cells (P<0.05). No other variable contributed significantly to the model.

Conclusions: Our data suggest that detection of CMV in the genital tract may contribute to the activation of the PD-1 axis on circulating T cells during suppressive ART. Because increased PD-1 on T cells has been implicated in the maintenance of the HIV reservoir, HIV disease progression and the inability of the immune system to adequately control HIV infection, future studies should examine whether CMV-dependent mechanisms play a role in T cell exhaustion.

301 HIV Myeloid Derived Suppressor Cells Control Cytomegalovirus Inflammation by IL-27

Ankita Garg; Stephen Spector
University of California San Diego, La Jolla, CA, US

Background: CMV is associated with persistent inflammation in HIV-infected persons. Here, we studied the effect of HIV expanded myeloid derived suppressor cells (MDSCs) in controlling CMV specific inflammation.

Methods: PBMCs from HIV–/CMV-seropositive (CMV+) donors were cultured in presence of heat inactivated HIV. After 5 days, $CD11b^+CD33^+CD14^+HLA\ DR^{hi}$ (DR^{hi} monocytes) and $CD11b^+CD33^+CD14^+HLA\ DR^{-/lo}$ (MDSCs) cell subsets were sorted by flow cytometry. B7H4 (a negative regulator of T cell function) was silenced using siRNA and cultured with/without autologous PBMCs in presence/absence of CMV pp65 peptides (pp65; 1μg/ml). In some experiments, PBMCs were cultured with HIV/pp65 in presence/absence of neutralizing anti-IL-27 antibody. Enumeration of B7H4 on MDSCs, regulatory T-cells, intracellular IFNγ, activated forms phospho(p)-Zap70 and p-Akt were determined by flow cytometry; IFNγ and IL-27 were quantified by ELISA. Data were analyzed using two-tailed, paired Student's *t* test.

Results: MDSCs cultured with autologous PBMCs exposed to pp65 caused a decrease in IFNγ production vs. controls or DR^{hi} monocytes (p=0.002). IFNγ release was restored when MDSCs were transfected with B7H4 siRNA and cultured with PBMCs in presence of pp65 (p=0.02). MDSCs cultured with PBMCs did not alter pp65 induced activation of proximal T-cell signaling molecule Zap70 but decreased activation of Akt; this was restored when B7H4 was knocked down in MDSCs cultured with PBMCs. Culture of MDSCs with pp65 produced more IL-27 vs. control MDSCs and DR^{hi} monocytes (p=0.05). Culture of CMV+ PBMCs with pp65 increased the frequency of $CD4^+IFN\gamma^+$ cells and release of IFNγ in supernatants vs. controls (p=0.04). IFNγ was further increased when PBMCs were cultured in presence of anti-IL-27 and stimulated with pp65; CMV– PBMCs did not produce IFNγ when treated with pp65. Furthermore, culture of CMV+ PBMCs with pp65 led to expansion of $FoxP3^+$ Tregs vs. controls (p=0.02) and CMV– (p=0.003); addition of anti-IL-27 had no effect on Treg expansion. Finally, HIV expanded MDSCs had increased expression of B7H4 when compared to DR^{hi} monocytes (p=0.03) which was inhibited in the presence of anti-IL-27 neutralizing antibody (p=0.05).

Conclusions: These findings suggest that IL-27 down regulates IFNγ during CMV infection. IL-27 induces B7H4 expression on HIV MDSCs which controls CMV induced T-cell IFNγ production by inhibiting p-Akt. IL-27 and B7H4 provide new therapeutic targets to control inflammation during HIV infection.

302 Persistent Elevation of Inflammation Markers in HIV+ Persons With CMV Disease

Melissa Schechter[1]; Bruno Andrade[2]; Eleanor M. Wilson[1]; Virginia Sheikh[2]; Sonya Krishnan[2]; Margaret Caplan[1]; Gregg Roby[2]; Adam Rupert[3]; Peter Burbelo[4]; Irini Sereti[2]
[1]NIAID, Leidos Biomedical Inc., Fredrick, MD, US; [2]National Institute of Allergy and Infectious Diseases, Bethesda, MD, US; [3]NIAID, Leidos Biomedical Inc., Fredrick, MD, US; [4]National Institute of Dental and Craniofacial Research, Bethesda, MD, US

Background: HIV+ individuals have a high prevalence of cytomegalovirus (CMV) co-infection and a minority of them develop CMV-associated end organ disease (EOD). CMV co-infection has also been associated with increased risk for cardiovascular events. The potential contribution of CMV infection or disease in chronic immune activation and non-infectious complications in HIV remains unclear.

Methods: In a case control study, HIV+ persons (CD4 <100 cells/μL pre-ART) with CMV EOD (N=25) or detectable CMV viremia (N=7) pre-ART were matched 1:1 by CD4 T-cell counts and age with HIV+ persons with undetectable CMV viremia by PCR. Participants were evaluated pre-ART (week 0) and at week (W) 12 and 48 after ART initiation. Cryopreserved plasma was used to measure markers of inflammation (CRP, IFN-γ, IL-12 p70, IL-10, IL-1β, IL-8, IL-6, TNF-α), monocyte activation and vascular injury (sICAM-3, E-Selectin, sCD14, sTF, MP-TF, CX3CL1, P-Selectin, Thrombomodulin, SAA, MCP-1, Eotaxin-3) and coagulation (D-dimer, Factor X Chromogenic, TF Chromogenic) by ELISA-based assays. Data were analyzed using Mann-Whitney and Spearman rank (correlation) tests.

Results: EOD cases were 66% male, with median age of 41 years, CD4 of 11 cells/μL, plasma HIV RNA of 5.12 $\log_{10}$ c/mL and CMV PCR 2.93 $\log_{10}$ c/mL units at W0. EOD cases had higher plasma levels of HIV RNA (p=0.01), CRP (p=0.03), IFN-γ (p=0.02), IL-10 (p=0.01), IL-8 (p=0.01), IL-6 (p=0.03), and SAA (p=0.001) compared to controls at W0. At W12, SAA (p=0.02), IFN-γ (p=0.0002), IL-10 (p=0.0003), IL-8 (p=0.01) and TNF-α (p=0.003) remained higher in EOD cases than in controls. At W48, IFN-γ (p=0.0.01), TNF-α (p=0.02) and IL-12 p70 (p=0.04) were persistently higher in EOD cases than in controls. Baseline, CMV IgG levels inversely correlated with sCD14 (r=-0.3, p=0.04), Fractalkine (r=-0.3, p=0.02) and HIV viral load (r=-0.33, p=0.01) but not with presence of EOD.

Conclusions: CMV end organ disease and viremia in HIV+ persons is associated with increased plasma levels of inflammatory and vascular injury biomarkers pre-ART with some persisting after ART. Our data suggest a protracted inflammatory response to CMV that may contribute to HIV pathogenesis and non-infectious complications.

Funded by NCI Contract No. HHSN261200800001E. This research was supported [in part] by the National Institute of Allergy and Infectious Diseases.

303 sCD163 Increase in HIV/CMV-Coinfected Subjects Included in ICONA Cohort

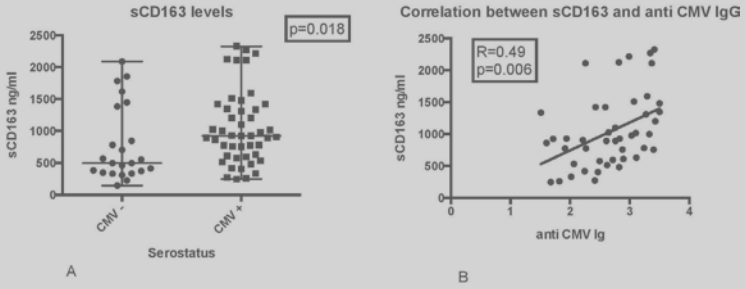
Serena Vita[3]; Miriam Lichtner[1]; Giulia Marchetti[2]; Claudia Mascia[3]; Esther Merlini[2]; Paola Cicconi[2]; Vincenzo Vullo[3]; Pier Luigi Viale[5]; Alberto Costantini[4]; Antonella d'Arminio Monforte[2]
For the Icona Foundation Study

[1]University of Rome La Sapienza, Polo Pontino, Latina, Italy; [2]San Paolo Hospital, Milano, Italy; [3]University of Rome La Sapienza, Rome, Italy; [4]University of Ancona, Ancona, Italy; [5]University of Bologna, Bologna, Italy

Background: Accumulating evidence suggest that inflammatory cytokines produced by monocytes/macrophages play a role in the vascular disease and cognitive decline**.** In HIV patients, herpes virus coinfection has been proposed as a key factor in sustaining immune activation, even in presence of HIV plasma viral control. In our previous study on the ICONA cohort we showed that in HIV patients (pts), CMV infection is an independent risk factor for non AIDS events/deaths.

Methods: We screened all the ICONA pts with an available CMV serology at enrolment (<= 6 months) and a plasma sample after ≥1 year of successful ART (defined as an undetectable HIV viral load and CD4+ count >200/mc). Pts were grouped according to CMV serostatus in CMV-infected (CMV+) (defined as CMV IgG positive) and CMV-uninfected (CMV-). Pts were also matched 2:1 for the following parameters: age, CD4 nadir, duration of HIV infection, HBV and HCV. We excluded pts with previous or current CMV organ diseases and other active organ disease in the previous 5 years. We detected sCD163, TNFα, sCD14, IL-6 using ELISA tests (R&D Systems) on plasma samples. All sample were retested for anti-CMV IgG (GenWay Biotech). Statistical analysis was performed using Mann-Withney Test and Spearman correlation analysis.

Results: A total of 69 subjects were recruited, 46 HIV monoinfected (CMV-) and 23 HIV/CMV (CMV+) coinfected. A higher median of sCD163 level (927.7 vs. 497.8 ng/ml, p=0.018) was found in CMV+ compared to CMV- group. TNFα, sCD14 were also elevated but didn't reach a significant difference in comparison to HIV/CMV- subjects. In HIV/CMV+ subjects a significant correlation was shown between anti-CMV IgG levels and sCD163 (r=0.49, p=0.006) (Fig.1). Moreover only in CMV+ subjects sCD163 levels were related to the duration of HIV infection (r=0.29, p=0.04). In the CMV positive group comparing CMV IgG levels with CD4 count, at the time of sampling, we found a significant negative correlation (r=0.39, p=0.0006).



Conclusions: CMV chronic infection appears to be linked to an increase in sCD163, a markers of myeloid activation, in HIV infected subjects under successful ART with controlled biological (age and sex) and HIV related (HIV suppression, CD4 nadir and CD4 recovery) factors. The persistent activation of monocytes and macrophages that has been implicated in the accelerated development of vascular and neurological disease in general population, may explain the increased risk of non AIDS events found in CMV/HIV coinfected subjects.

304 Genital CMV Shedding Predicts Syphilis Acquisition in HIV-Infected MSM on ART

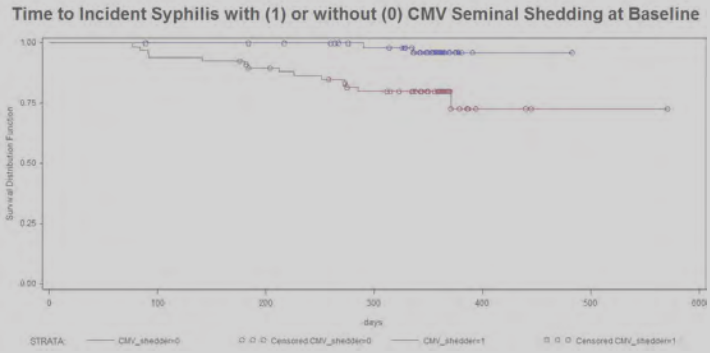
Sara Gianella Weibel[1]; David M. Smith[1]; Eric Daar[2]; Michael Dube[3]; Andrea Lisco[4]; Christophe Vanpouille[5]; Richard Haubrich[1]; Sheldon Morris[1]

[1]University of California San Diego, La Jolla, CA, US; [2]Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, US; [3]University of Southern California Keck School of Medicine, Los Angeles, CA, US; [4]National Institute of Allergy and Infectious Diseases, Bethesda, MD, US; [5]National Institute of Child Health and Human Development, Bethesda, MD, US

Background: Bacterial sexually transmitted infections (STI) are highly prevalent among HIV-infected men who have sex with men (MSM) and are co-factors in HIV transmission. While sexual behavior and networks are important in STI acquisition, other biological factors have not been emphasized as targets for intervention.

Methods: As part of a behavioral intervention, 136 HIV-infected MSM on suppressive (<500 copies/ml) ART were followed for 12 months and screened for incident bacterial STI (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and syphilis*)* every three months. Baseline predictors of bacterial STI were determined using survival analysis of time to incident STI. Tested variables at baseline included: behavioral factors (number of sex partners, number of anal sex acts, use of methamphetamine and other drugs), plasma HIV RNA levels, current and nadir CD4 T and CD8 T cell count, genital shedding of herpes viruses (CMV, EBV, HSV, HHV-6, -7, and -8), serum CMV IgG levels, and soluble markers of genital inflammation (MCP-1, IL-6, TNF-alfa, Interferon-gamma, RANTES and IP-10 in baseline seminal plasma).

Results: Thirty-four subjects (26.2%) acquired bacterial STIs during follow-up, sometimes with more than one pathogen (16 syphilis, 20 gonorrhea, 14 chlamydia). Acquisition of syphilis during follow-up was associated with genital CMV shedding at baseline (21% in CMV shedders versus 3% in non-shedders, P=0.003, see figure attached), younger age (P=0.005) and more sex partners (P=0.047). None of the tested variables except partner number was associated with acquisition of other STIs (chlamydia and gonorrhea at any site). For the acquisition of syphilis, in multivariable Cox-proportional hazard model adjusted hazard rates were as follows: baseline CMV shedding 4.87 (95% CI 1.06-22.47), age 0.96 (per year younger [95% 0.91-1.01]) and number of partners past month 1.06 (per partner per month [0.99-1.13]). Also, syphilis cases compared to non-cases had lower baseline levels of seminal MCP-1 (P=0.01), and lower seminal MCP-1 levels were associated with higher levels of seminal CMV DNA (P=0.005).



Kaplan-Meier Plot showing incidence of Syphilis acquisition in participant with (1) and without (0) CMV seminal shedding at baseline.

Conclusions: In this prospective study, presence of genital CMV shedding at baseline was strongly associated with acquisition of syphilis. Lower level of seminal MCP-1 was associated with both presence of genital CMV shedding and syphilis acquisition. Future studies with anti-CMV therapeutics could help determine underlying mechanisms and if causal associations exist.

392 Defective HIV-1 Proviruses Can Be Transcribed Upon Activation

Ya-Chi Ho; Ross Pollack; Patrick Yong; Robert F. Siliciano

Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: HIV-1 persists in the latent reservoir, primarily resting memory CD4+ T cells, as integrated proviruses. The majority of these proviruses are defective, containing large internal deletions or APOBEC-mediated G-to-A hypermutations. However, we previously found that even if the HIV-1 genome contains lethal mutations, the LTR promoter may remain intact, indicating that HIV-1 RNA may still be transcribed. The transcription of HIV-1 RNAs from defective proviruses may complicate the measurement of the size of the latent reservoir using latency reversing agents during the shock-and-kill strategy, as measurement of the defective proviral RNA does not indicate the reactivation of the clinically significant replication-competent proviruses. Further, whether the cells harboring defective proviruses would expand upon reactivation, or would be eliminated by cytolytic T cells (CTLs), remains unknown.

Methods: Resting CD4+ T cells from aviremic patients under suppressive antiretroviral therapy are activated with CD3/CD28 costimulation under enfurvitide to prevent new rounds of in vitro infection. Autologous CTLs were stimulated with Group M Consensus Gag peptide mixture and IL-2. To examine whether cells containing intact or defective HIV-1 can be eliminated by CTLs, we co-cultured pre-stimulated autologous CTLs with activated CD4+ T cells. Cell-associated RNA and proviral DNA from cells which are resting, activated, and CTL co-cultured was subjected to quantitative PCR and deep-sequencing of the Gag region to examine the start codon of Gag and two tryptophan residues, which are hotspots APOBEC-mediated hypermutations. CTLs were removed by magnetic bead depletion from the CTL-CD4 coculture before qPCR for normalization to CD4 cell count.

Results: We found a significant proportion of the HIV-1 RNA in activated patient CD4+ T cells contains lethal mutations. The amount of defective proviruses increased over the course of activation, indicating expansion of cells containing defective proviruses upon stimulation. The percentage of defective proviruses increased, implying the effect of viral cytopathic effects by reactivated intact proviruses. The amount of HIV-1 proviruses, both intact and defective, decreased after addition of CTLs in some patients, indicating possible elimination by CTLs.

Conclusions: Defective HIV-1 proviruses may be transcribed during latency reversal. Cells containing defective HIV-1 proviruses may expand under T cell activation.

391 Influenza Vaccination Increases HIV-1 Transcription During Antiretroviral Therapy

Christina C. Yek[1]; Sara Gianella[1]; Montserrat Plana[2]; Pedro Castro[2]; Felipe Garcia[2]; Marta Massanella[1]; David M. Smith[1]

[1]*University of California San Diego, San Diego, CA, US;* [2]*University of Barcelona, Barcelona, Spain*

Background: Curative strategies using stimulators such as histone deacetylase inhibitors, disulfiram and IL-7 to reactivate HIV have thus far demonstrated only modest activity. In contrast, transient increases in viremia after administration of standard vaccines have been observed even during antiretroviral therapy (ART). In this study we investigate whether routine influenza vaccination can reactivate HIV.

Methods: Eleven HIV-infected individuals on suppressive ART (<50 copies/ml) were selected from the intervention arm of a randomized trial that studied the effects of a vaccination schedule on viral rebound after structured treatment interruption (NCT00329251). Blood samples were obtained at baseline and 1 month after influenza vaccination. DNA and RNA were extracted from cryopreserved peripheral blood mononuclear cells using a Qiagen AllPrep DNA/RNA Mini Kit. Cell-assoiated HIV DNA and RNA transcripts were quantified by droplet digital PCR using primers for *gag* and 2-LTR (for HIV DNA), unspliced *gag* RNA (HIV usRNA), multispliced *tat-rev* RNA (HIV msRNA), polyA and RPP30 (cellular marker for normalization). Values were adjusted for percentage of CD4 T cells as measured by flow cytometry.

Results: Nine of 11 subjects showed an increase in HIV usRNA after influenza vaccination despite undetectable viral loads throughout. Median HIV usRNA levels pre- and post-vaccination were 28.7 [4.2-56.4] and 91.0 [43.2-173.1] copies/10^6 CD4 T cells, respectively ($p=0.049$). Mean increase in HIV usRNA after vaccination ranged from 0 to 49-fold (mean 10.6). No significant changes were observed in HIV msRNA ($p=0.25$), polyA ($p=0.91$), total HIV DNA ($p=0.15$), or 2-LTR circle copies ($p=0.74$).

Conclusions: This study demonstrated a clear increase in cell-associated HIV usRNA 1 month after influenza vaccination, consistent with antigenic stimulation of the HIV reservoir during suppressive ART. The mean 10.6-fold increase in HIV usRNA is comparable to or better than that seen with administration of Vorinostat. Total HIV DNA and 2-LTR circles did not change, suggesting reactivation of replication-incompetent virus and/or ART-mediated suppression of viral propagation. Although we do not propose that standard vaccinations will cure HIV, these findings suggest that a component of immune stimulation could be considered in the development of eradication strategies.

427 Measurements of Viral Transcription in Elite Suppressor CD4+ T Cells

Christopher W. Pohlmeyer; C. Korin Bullen; Greg Laird; Alyssa R. Martin; Victoria Walker-Sperling; Stanley U. Chioma; Robert F. Siliciano; Joel Blankson

Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: Elite suppressors (ES) are patients who control HIV replication without antiretroviral therapy. Prior studies have shown that the frequency of latently infected cells in these patients is much lower than patients on suppressive antiretroviral regimens. However the frequency of CD4+ T cells that express HIV-1 mRNA at baseline and following T cell stimulation is unknown. In this study we compared HIV-1 transcription levels in CD4+ T cells from chronic progressors (CPs) on suppressive antiretroviral regimens and ES.

Methods: To measure intracellular HIV-1 mRNA, we isolated CD4 T cells from PBMCs of ES and CPs. Replicates of $5x10^6$ cells were stimulated with PMA/ionomycin or DMSO for 24 hours. The cells were collected and lysed in Trizol for RNA extraction and subsequent quantification by qPCR. RNA from supernatants were collected and measured for released HIV-1 mRNA.

Results: A comparison of cell associated HIV-1 mRNA in CD4+ T cells of HAART-suppressed CPs and ES shows that ES have significantly less HIV-1 mRNA per $5x10^6$ cells before stimulation. HIV1 mRNA was uniformly detected in CPs, but was present at very low levels in just 2 of 8 ES ($p>0.05$). When $5x10^6$ CD4+ T cells were stimulated with PMA/ionomycin, the levels of cell-associated HIV-1 mRNA increased in 4 of 7 ES. Additionally, when measuring HIV-1 mRNA levels in culture supernatant following stimulation of 5×10^6 CD4+ T cells with PMA/ionomycin, we detected release of virus from just 2 of 8 ES compared to 5 of 5 CPs. When more replicates were analyzed, viral release was seen in 4 ES. 2 of these patients showed positivity in 1 of 5 replicates ($25x10^6$ cells), releasing approximately 3,000 and 5,000 copies HIV-1 RNA each. Poisson statistics suggests an 89% chance that the signal observed reflects a single cell releasing virus, and our HIV-1 mRNA measurements fit with current estimates of the burst size of an infected CD4+ T cell.

Conclusions: In the present study, we demonstrate that the baseline levels of cell associated HIV-1 mRNA in ES are significantly lower than those observed in CPs per $5x10^6$ cells. However an increase in viral transcription following T cell stimulation was observed. These results further characterize the size of the latent reservoir in ES and confirm earlier studies that suggested that some of these patients are infected with replication-competent virus.

384 Minor Contribution of Host-HIV Readthrough Transcripts to the Level of HIV-1 *gag* RNA

Alexander Pasternak[1]; Una O'Doherty[2]; Ben Berkhout[1]

[1]*Academic Medical Center University of Amsterdam, Amsterdam, Netherlands;* [2]*University of Pennsylvania, Philadelphia, PA, US*

Background: Cell-associated (CA) HIV-1 unspliced RNA is an important marker of the viral reservoir and the response to antiretroviral therapy (ART). Recently it has been used in clinical trials as a measure of virus activation by latency-reversing agents. Primers specific for the HIV *gag* regions are frequently used in PCR-based assays that quantify unspliced RNA. However, because HIV-1 integrates within actively transcribed host genes, it has been suggested that some of the transcripts detected by the *gag*-specific assays may not represent genuine HIV RNA but rather chimeric host-HIV readthrough transcripts. To properly interpret the results of the *gag* assays, it is necessary to determine the relative contribution of such readthrough transcripts to the HIV *gag* RNA in ART-treated patients.

Methods: We developed a sensitive nested real-time PCR assay that amplifies the 5' LTR-encoded U3 – packaging signal region (U3-Psi) of HIV-1. This assay specifically measures host-HIV readthrough transcripts but does not detect genuine HIV-1 unspliced RNA (Fig. 1). Total DNA and total RNA were isolated from PBMC samples of 48 ART-treated patients whose plasma viremia had been undetectable (<40 copies/ml) for ≥1 year prior to the study. CA HIV-1 DNA and RNA were separately quantified in these samples using both the U3-Psi assay and the seminested real-time PCR assay specific for the HIV-1 *gag* region. The sensitivity of both assays is 4 copies/reaction. The same inputs of DNA or RNA were used for both assays.

Results: As expected, both U3-Psi and *gag* assays detected HIV-1 DNA in >90% of the patients (44/48 and 46/48, respectively) with no significant quantitative bias between the assays, demonstrating the functionality of the U3-Psi assay. HIV-1 *gag* RNA was detected in 44/48 of these patients (92%) with the median copy number of 590 (interquartile range, 217-1194) copies/μg total RNA. However, the detectability of readthrough RNA was only 40% (19/48 patients). In the 19 patients where the readthrough RNA was detected, its copy number was 49 (41-122) copies/μg total RNA, representing only 8.3% (2.4%-11.2%) of the HIV-1 *gag* RNA. Notably, the real readthrough/*gag* RNA ratio is much lower, as patients with undetectable readthrough RNA (60% of all patients) were excluded from this calculation.

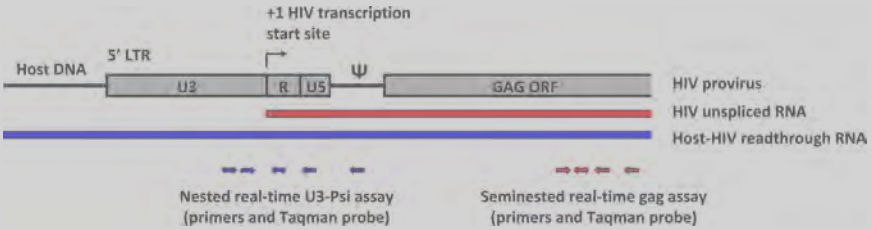


Figure 1. Schematic representation of real-time PCR assays for the detection of readthrough and *gag* RNA. LTR, long terminal repeat; ORF, open reading frame; Ψ, HIV packaging signal (Psi).

Conclusions: We observed only a minor contribution of host-HIV-1 readthrough transcripts to the level of HIV-1 *gag* RNA. The vast majority of HIV-1 *gag* RNA transcripts in ART-treated patients represent genuine HIV-1 unspliced RNA.

379 Characterizing the Active HIV Reservoir on ART: Cell-Associated HIV RNA and Viremia

Feiyu Hong; Elizabeth Fyne; Anthony R. Cillo; Margaret A. Bedison; Dianna Koontz; John W. Mellors

University of Pittsburgh, Pittsburgh, PA, US

Background: Despite combination antiretroviral therapy (ART), HIV-1 RNA can be detected in plasma and peripheral blood mononuclear cells (PBMCs), indicating proviral transcription and production of virions, i.e. an active reservoir of HIV. It is not known whether proviral copy number, HIV-1 transcription, and residual plasma viremia on ART are related.

Methods: We conducted a cross-sectional study of viremic patients off ART and of virologically suppressed (<50 cps/ml) patients on ART. PBMCs were tested for total cell-associated (CA) HIV-1 DNA and unspliced HIV-1 RNA using sensitive qPCR targeting 3' pol. Plasma was tested for residual viremia by single copy assay targeting the same pol region. Unpaired t-test was used to compare viremic and patients on ART. Correlations between plasma viremia and cellular nucleic acids were assessed with Pearson's coefficient.

Results: 12 viremic patients and 23 patients on ART were studied. In patients on ART, median CA HIV-1 DNA was 310 copies/10^6 PBMCs (range: 45, 984) and median CA HIV-1 RNA was 59 copies/10^6 PBMCs (range: 1, 454), both were significantly lower than in viremic patients (median 565 [range: 48, 4680], $p = 0.033$; median 296 [range: 33, 19172], $p = 0.030$; for CA HIV-1 DNA and RNA, respectively). The 5-fold reduction in CA HIV-1 RNA on ART is small compared with the $> 4 \log_{10}$ difference in plasma viremia between these two groups (median 0.44 [range: 0.4, 26] vs. 10542 [range: 564, 474211] copies/mL on and off ART, respectively), indicating substantial persistence of HIV-1 transcription despite ART. A strong, positive correlation was detected between cell-associated HIV-1 DNA and unspliced RNA in both viremic (Pearson's $r = 0.974$; $p < 0.001$) and patients on ART ($r = 0.779$; $p < 0.001$). In viremic patients, the levels of plasma HIV-1 RNA also show strong, positive correlations with cell-associated HIV-1 DNA and RNA (Pearson's $r = 0.849$ and 0.843, respectively; $p < 0.001$). By contrast, in patients on ART, residual plasma viremia was not correlated with cell-associated HIV-1 DNA ($r = 0.06$; $p = 0.78$) or RNA ($r = -0.18$; $p = 0.39$).

Conclusions: This is the first study to show i) a strong, positive correlation between the number of HIV-infected cells and the level of cell-associated HIV-1 RNA in patients on ART, and ii) no correlation between cell-associated HIV-1 RNA and the levels of persistent viremia. These findings suggest that most of persistent HIV-1 transcription in patients on ART does not result in viremia.

390 Nascent LTR-Driven Transcription Can Lead to Translation of HIV Proteins in Resting CD4+ T Cells

Laura DeMaster[1]; Alexander Pasternak[2]; Una O'Doherty[1]

[1]*University of Pennsylvania, Philadelphia, PA, US;* [2]*Academic Medical Center University of Amsterdam, Amsterdam, Netherlands*

Background: We have previously described a model of direct infection of resting CD4+ T cells and contrasted it with models of activated CD4+ T cell infection. We found that infected resting CD4 cells express low levels of viral protein without releasing infectious virus, raising the possibility that reservoirs may express HIV proteins in vivo and be visible to the immune system. Unspliced RNA (usRNA) encoding gag was the predominant HIV RNA form detected in infected resting cells. We designed experiments to ask if nascent transcription occurs in resting CD4+ T cells or if the Gag signal detected is due to an artifact such as read-through transcription or incoming virus.

Methods: To address the contribution of incoming virus to Gag signal, we first sorted Gag+ and Gag-negative cells from cultures infected in vitro and measured levels of HIV DNA in both populations, similar to an approach we used in vivo. RT-PCR and FACS analysis were used to determine whether other viral proteins (made from spliced RNA forms) were present in cells infected in vitro and in CD4+ T cells from ART patients. In addition, given that tat/rev is present at very low levels in vivo in patients on ART, we asked if tat/rev is required for LTR driven expression.

Results: We found that Gag+ cells were strongly (more than 100-fold) enriched for HIV DNA compared to Gag-negative cells in infected cultures. In addition to spliced HIV RNA forms, further evidence of nascent transcription included direct and indirect evidence of new synthesis of multiple HIV proteins by FACS. Read-through transcripts were detectable but present at low levels compared to gag RNA in both cells infected in vitro and in CD4 cells from ART patients. Stimuli such as IL-7 and Romidepsin preferentially induced gag usRNA over read-through transcripts. In contrast, SAHA induced both read-through and gag usRNA transcription two-fold. Notably, we show that low-level protein expression can occur in the absence of tat/rev using a viral vector with a deletion of tat/rev gene expression.

Conclusions: Nascent LTR transcription occurs in HIV-infected resting CD4+ T cells. In vitro and in vivo data suggest that Gag is the predominant transcript (usRNA) and protein expressed in HIV infected individuals on ART. The relative contributions of replication competent and defective proviruses to viral protein expression in vivo remain undefined.

778 Obesity and Inflammation in Resource-Diverse Settings of ART Initiation

Kristine M. Erlandson[1]; Nikhil Gupte[2]; Javier R. Lama[3]; Patcharaphan Sugandhavesa[4]; Thando Mwelase[5]; Ashwin Balagopal[2]; David Asmuth[6]; Thomas B. Campbell[1]; Amita Gupta[2]
On behalf of the A5175 and NWCS319 study team

[1]University of Colorado, Aurora, CO, US; [2]Johns Hopkins University, Baltimore, MD, US; [3]Impacta Peru Clinical Trials Unit, Lima, Peru; [4]Chiang Mai University, Chiang Mai, Thailand; [5]University of Witswatersrand, Johannesburg, South Africa; [6]University of California Davis, Sacramento, CA, US

Background: The heightened inflammatory profile resulting from both HIV infection and obesity is of increasing importance in many HIV-related comorbidities. Little is known about the association between the change in body mass index (BMI) with antiretroviral (ART) initiation and the change in inflammatory markers, particularly in resource-limited settings.

Methods: AIDS Clinical Trials Group study A5175 was a randomized trial comparing 3 ART regimens in resource-diverse international settings; the following is a country stratified random sub-cohort of 270 subjects; 246 subjects had stored samples. BMI (weight [kg]/height [m]^2) was categorized as underweight (UW, <18.5), normal weight (NW, 18.5-24.9), and overweight/obese (OW/OB, ≥25.0). Inflammatory markers were measured (TNF-α, IFN-γ, IL-6, IL-18, IP-10, CRP, sCD14) at weeks 0, 24, 48. Effect of baseline and change in BMI on changes in biomarkers was assessed using random effects models fitted for natural spline at BMI categories and adjusted for age, sex, country, $\log_{10}$ HIV-1 RNA, and treatment arm. A separate model assessed the effect of change to OB BMI (>30 versus ≤30).

Results: Of 246 participants, 50% were female, 53% black, with a median age 35 and CD4 count 179. 37% were assigned to ZDV/3TC+EFV, 33% to ATV+FTC+DDI, and 30% to TDF/FTC+EFV. At week 0, 8% were UW, 65% NW, 27% OW/OB including 7% OB; at week 48, 3% were UW, 60% NW, 37% OW/OB including 9% OB. In multivariate analyses, among baseline UW subjects, an incremental BMI increase was associated with decreased CRP (β -9.32; p=0.001) and trend towards decreased sCD14 (β -0.09; p=0.09). For baseline OW/OB subjects, an increase in BMI was associated with increased sCD14 (β 0.02; p=0.05). No significant associations were detected in the NW group or within other inflammatory markers (p>0.05). In multivariate analyses comparing OB vs not OB participants, OB was associated with an increase in sCD14 (β 0.19; p=0.02) and trend towards higher IL-18 (β 127.7; p=0.056); there were no associations with other markers.

Conclusions: Among HIV-infected persons initiating ART in resource-diverse settings, weight gain among underweight persons may reduce inflammation. In contrast, weight gain among obese persons appeared to heighten inflammation. As sCD14 is a marker of mortality during HIV treatment, the data highlight the potential impact of obesity on treatment outcomes. Further investigation into the impact of obesity on HIV treatment outcomes in resource-limited settings is needed.

779 Body Composition Outcomes at 96 Weeks in the SECOND-LINE RCT DXA Substudy

Mark A. Boyd[1]; Janaki Amin[1]; Patrick W. Mallon[2]; Jennifer F. Hoy[3]; Samuel Ferret[4]; Waldo Belloso[5]; Praphan Phanuphak[6]; Sean Emery[1]; David A. Cooper[1]
SECOND-LINE study group

[1]University of New South Wales Australia, Sydney, Australia; [2]University College Dublin, Dublin, Ireland; [3]Monash University/Alfred Hospital, Melbourne, Australia; [4]Hopital Saint Louis, Paris, France; [5]Hospital Italiano, Buenos Aires, Argentina; [6]Thai Red Cross AIDS Research Centre, Bangkok, Thailand

Background: Antiretroviral therapy (ART) should optimally cause minimal harm. Preferred N(t)RTI-backbones are associated with toxicities with poorly understood long term consequences. In the SECOND-LINE study we demonstrated non-inferiority (margin=12%) of ritonavir-boosted lopinavir (r/LPV) plus raltegravir (RAL-arm) compared to r/LPV plus 2-3N(t)RTI regimen (N(t)RTI-arm) after virological failure of standard NNRTI+2N(t)RTI first-line ART. The RAL-arm was associated with significantly less bone mineral density (BMD) loss. We hypothesised that the RAL-arm would be associated with a greater degree of limb fat gain at 96 weeks.

Methods: We performed a DXA-substudy of SECOND-LINE at weeks 0, 48 and 96 at 8 sites in Argentina, India, Malaysia, South Africa and Thailand. Primary endpoint was the mean percent change from baseline in peripheral limb fat. Analysis was by intention to treat (ITT). We adjusted for baseline imbalances in sex, BMI and smoking. Multivariate linear regression was used to assess between-group differences and predictors of percent change in limb fat mass. Results are mean (SD) and median (IQR).

Results: Baseline characteristics of the 210 enrolled participants: 110 (52%) female, age 38.6 (7.8) years, 52% Asian/43% African, HIV RNA 4.1 (1.0) $\log_{10}$ copies/mL, CD4+ count 220 (167) cells/μL, first-line ART duration 3.3 (1.9-5.9) years, 34%% and 48% on d4T and AZT respectively prior to initiating randomised ART. Eighty six percent and 42% N(t)RTI arm study participants received TDF and AZT respectively. After 96 weeks the mean (SD)% limb fat change from baseline was 16.8 (32.6)% in the N(t)RTI-arm and 28.0 (37.6)% in the RAL-arm, a mean difference (95% CI) of 10.2 (0.1-20.4)% (p=0.048). Baseline predictors of percent changes in limb fat mass over 96 weeks are shown in Table 1.

Table 1. Multivariate baseline predictors of percent change in limb fat mass over 96 weeks

Covariate		Reference	N	Coefficient	95% CI	P-value	Overall p-value
Study arm	RAL-arm	*N(t)RTI-arm*	105	4.9	-2.6, 12.5	0.2	
Sex	Female	*Male*	101	15.0	4.2, 25.9	0.007	
BMI (kg/m^2)			192	1.5	0.5, 2.5	0.005	
BMI change over 96 weeks (kg/m^2)			192	8.4	6.9, 9.8	<0.001	
Baseline limb fat mass (kg)							
	3.9 - 6.9	*0.7 - 3.89*	45	-19.6	-30.8, -8.4	0.001	
	7.0 - 11.0	*0.7 - 3.89*	49	-36.4	-50.0, -22.8	<0.001	
	11.1 - 32.0	*0.7 -3.89*	52	-28.1	-76.8, -41.2	<0.001	<0.001
Ethnicity							
	African	*Asian*	83	-9.8	-19.5, -0.1	0.048	
Total ta-NRTI (AZT/d4T) duration prior to study (years)			192	-4.0	-8.0, 0.02	0.051	

Conclusions: Although N(t)RTI-sparing in SECOND-LINE was associated with improved peripheral limb fat gain over 96 weeks, it was not significant after adjustment for other predictors on multivariate analysis. Significant predictors of peripheral fat gain were female sex, higher baseline BMI and a greater increase in BMI. Africans were more likely to lose limb fat than Asians. Those with more limb fat at baseline were more likely to lose limb fat over 96 weeks. Thymidine-analogue duration prior to study had a borderline association with less peripheral fat gain.

780 Bone Quality by Quantitative Ultrasound at the Radius Does Not Differ in ART-Naïve HIV+ and HIV- Rwandan Women

Eugene Mutimura[1]; Qiuhu Shi[2]; Donald R. Hoover[3]; Kathryn Anastos[4]; Emmanuel Rudakemwa[5]; Jean Claude Dusingize[1]; Jean D'Amour Sinayobye[1]; Michael T Yin[6]

[1]Regional Alliance for Sustainable Development, Kigali, Rwanda; [2]School of Health Sciences and Practice, New York Medical College, New York, NY, US; [3]State University of New Jersey, New Brunswick, NJ, US; [4]Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, US; [5]King Faisal Hospital, Kigali, Rwanda; [6]Columbia University Medical Center, New York, NY, US

Background: Fracture incidence appears to be increased in HIV+ individuals, especially after ART. Dual-energy x-ray absorptiometry (DXA) characterizes bone mineral density (BMD) and is predictive of fracture, but is not widely available in resource-constrained settings (RCS). Quantitative ultrasound (QUS) assesses bone quality by measuring speed of an ultrasound wave (SOS) through bone; lower SOS is predictive of increased fracture risk in older women. We compared bone quality by QUS at the radius in HIV+ and HIV- women in Rwanda.

Methods: Cross sectional study of 646 ART-naïve HIV+ and 211 HIV- women. Demographic, anthropomorphic, laboratory, co-morbidity, and socioeconomic data were collected. A Sunlight Omnisense 7000 QUS (BeamMed Ltd, Israel) was utilized to measure SOS at the radius using 2 trained technicians. Inter-observer agreement assessed on a subset (N=56) was high (kappa>0.90). Mean SOS±SD, T-scores (compared to SOS from young women), Z- scores (compared to SOS from women of same age) using the manufacturer's reference based upon American norms were calculated.

Results: HIV+ women were younger than HIV- women (35±7 vs 42+10 years, p<0.001), had more chronic diarrhea (23% vs 8%, p<0.001), and lower albumin (3.4±0.7 vs. 3.9±0.5 g/dL, p<0.001), but similar body mass index (BMI, 21.5±3.7 vs 21.3±3.8 kg/m^2, p=0.51). Among HIV+ women, mean CD4+ T cell count was 285 (SD=166) cells/mm^3 and 30% had an AIDS defining illness. Average SOS was slightly higher in HIV+ than HIV- women (4024.4±110.5 vs. 4003.9±113.1 m/s, p= 0.02); this group difference was attenuated by adjustment for age (p=0.04) but not BMI (Table). SOS T- and Z-scores did not differ pre or post adjustment for BMI between HIV infection groups. Among HIV+ women, SOS did not differ by CD4+ count <200 vs. ≥200cells/mm^3: 4016±117 vs 4028±107m/s, respectively (p=0.19).

Conclusions: Despite having relatively advanced HIV disease, ART-naïve, predominantly premenopausal Rwandan women did not have worse bone quality by radius QUS than uninfected controls. Our results are consistent with data from a South African study that found that BMD by DXA were similar in ART-naïve HIV+ women and uninfected controls. Unlike DXA, radius QUS is uninfluenced by weight or body fat, is portable, inexpensive, and does not emit radiation or require high-level training. QUS may be an ideal modality to track bone quality and fracture risk after ART-initiation in HIV+ individuals in RCS.

Bone Quality by Quantitative Ultrasound among ART-naïve HIV+ and HIV- Rwandan women

Characteristics	HIV+ (N=646)	HIV- (N=211)	P value	P value Adjusted for Age	P value Adjusted for BMI
Average SOS (m/s)	4024.4±110.5	4003.9±113.1	0.02	0.04	0.02
T score	-0.07±1.37	-0.18±1.43	0.30	-	0.31
Z score	0.09±1.35	0.10±1.38	0.90	-	0.89

Data are presented as Mean±SD; *The p-value is from ANOVA; ART, antiretroviral therapy; HIV+, HIV-infected; HIV, HIV-uninfected; BMI, Body mass index; SOS, ultrasound wave.

Conclusions: Despite having relatively advanced HIV disease, ART-naïve, predominantly premenopausal Rwandan women did not have worse bone quality by radius QUS than uninfected controls. Our results are consistent with data from a South African study that found that BMD by DXA were similar in ART-naïve HIV+ women and uninfected controls. Unlike DXA, radius QUS is uninfluenced by weight or body fat, is portable, inexpensive, and does not emit radiation or require high-level training. QUS may be an ideal modality to track bone quality and fracture risk after ART-initiation in HIV+ individuals in RCS.

781 Predictors and Outcomes of Incident High Cholesterol in Adults on ART in South Africa

Denise Evans[1]; Alana T. Brennan[2]; Faith Moyo[1]; David Spencer[3]; Kay Mahomed[3]; Mhairi Maskew[1]; Lawrence Long[1]; Sydney Rosen[2]; **Matt P. Fox**[2]

[1]University of the Witwatersrand, Johannesburg, South Africa; [2]Boston University, Boston, MA, US; [3]Right to Care, Johannesburg, South Africa

Background: As the HIV-infected population ages in sub-Saharan Africa, non-communicable chronic disease incidence among patients on ART is likely to rise. Specific antiretroviral drugs are considered independent risk factors for cardiovascular disease (CVD), and high total cholesterol (TC) is a risk factor for CVD, stroke and renal disease. We examined predictors of high TC in ART patients in South Africa.

Methods: Prospective study of HIV-positive, ART-naïve adults initiating ART at a large urban clinic in Johannesburg from 04/04 to 07/12. Patients with TC ≥6mg/dl at ART initiation were excluded. We defined incident high cholesterol as a TC ≥6mg/dl and categorized it as (i) one elevated TC, (ii) elevated TC with repeat TC <6mg/dl or (ii) elevated TC with repeat ≥6mg/dl. Cox regression was used to identify variables at ART initiation associated with incident high TC. Person-time started at ART initiation and ended at the earliest of high TC, death, loss to follow up (LTF; >3 months late for next scheduled visit), transfer, completion of 24 months of follow-up, or dataset closure (07/2014).

Results: Among 18,998 eligible patients, 2990 (16%) had a high TC by 24 months on ART. Of these, 488 (16%) had no repeat TC, 1323 (44%) had a repeat TC <6mg/dl, and 1179 (40%) had a persistently high TC ≥6mg/dl. Regression models showed patients ≥40 vs. <40 years, those with a CD4 count <100 vs. ≥100cells/mm^3 or BMI ≥25 vs. <25kg/m^2 at ART initiation had an increased hazard of high TC over the first 24 months on ART (Table).

Of the 2990 patients with a high TC, 5% died, 7% were LTF and 11% developed moderate or severe renal insufficiency (creatinine clearance <60ml/min). Among those with a repeat TC, rates of mortality (0.82 vs. 0.83/100pys) and LTF (6.1 vs. 7.3/100pys) after high TC were similar for those with incident high TC and a repeat TC <6mg/dl compared to those with a persistently high TC ≥6mg/dl. However, those with persistently high TC ≥6mg/dl had a higher rate of renal insufficiency (CrCl <90ml/min) (19.0/100pys) after high TC compared to those who reduced their TC <6mg/dl (16.0/100pys). 31% of patients with a high TC changed a single drug, mainly from d4T to TDF or ABC, while 29% were prescribed cholesterol lowering drugs and 13% had both.

Table 1. Predictors of high total serum cholesterol after 24 months on antiretroviral therapy at Themba Lethu Clinic, Johannesburg, South Africa (n=18,998).

		One elevated TC		Elevated TC + repeat <6mg/dl		Elevated TC + repeat ≥6mg/dl	
		No. Events N, %	Adjusted HR 95% CI	No. Events N, %	Adjusted HR 95% CI	No. Events N, %	Adjusted HR 95% CI
Initiating NRTI	TDF	147 (2.9%)	1.0	171 (3.4%)	1.0	130 (2.6%)	1.0
	d4T	327 (2.5%)	0.86 (0.67-1.10)	1114 (8.4%)	2.41 (1.99-2.96)	1026 (7.7%)	3.48 (2.73-4.44)
Initiating NNRTI	EFV	433 (2.6%)	1.0	1170 (6.9%)	1.0	1075 (6.4%)	1.0
	NVP	39 (3.0%)	1.16 (0.79-1.69)	95 (7.3%)	1.00 (0.79-1.27)	62 (4.7%)	0.83 (0.62-1.10)
Age at ART initiation (years)	18-29.9	79 (2.1%)	1.0	204 (5.4%)	1.0	133 (3.5%)	1.0
	30-39.9	188 (2.2%)	1.08 (0.78-1.39)	587 (7.0%)	1.19 (1.00-1.41)	428 (5.1%)	1.44 (1.16-1.79)
	≥40	221 (3.3%)	1.68 (1.26-2.24)	530 (7.9%)	1.57 (1.31-1.87)	618 (9.2%)	2.88 (2.33-3.56)
Sex	Female	312 (2.6%)	1	884 (7.5%)	1.0	772 (6.5%)	1.0
	Male	176 (2.5%)	0.99 (0.80-1.22)	439 (6.1%)	0.89 (0.78-1.02)	407 (5.7%)	0.88 (0.77-1.01)
Body mass index (kg/m²)	<18	46 (1.8%)	0.80 (0.57-1.12)	127 (4.8%)	0.81 (0.66-0.99)	97 (3.7%)	0.65 (0.52-0.82)
	18-24.9	272 (2.7%)	1.0	693 (6.9%)	1.0	631 (6.3%)	1.0
	25-29.9	96 (3.4%)	1.29 (1.00-1.66)	292 (10.2%)	1.54 (1.33-1.79)	261 (9.1%)	1.45 (1.24-1.70)
	≥30	49 (3.5%)	1.31 (0.93-1.85)	134 (9.5%)	1.47 (1.19-1.81)	125 (8.9%)	1.55 (1.25-1.92)
CD4 count (cells/mm³)	>200	92 (3.2%)	1.0	167 (5.9%)	1.0	143 (5.0%)	1.0
	101-200	177 (2.8%)	0.98 (0.75-1.29)	459 (7.3%)	1.15 (0.95-1.40)	411 (6.5%)	1.07 (0.87-1.32)
	51-100	70 (2.0%)	0.70 (0.50-0.99)	295 (8.4%)	1.41 (1.14-1.74)	240 (6.8%)	1.19 (0.95-1.49)
	0-50	134 (2.5%)	1.06 (0.89-1.42)	372 (6.8%)	1.36 (1.11-1.66)	358 (6.6%)	1.39 (1.13-1.72)
Hemoglobin (g/dl)	≥10	365 (2.8%)	1.0	998 (7.7%)	1.0	892 (6.9%)	1.0
	<10	86 (2.0%)	0.98 (0.77-1.27)	236 (5.5%)	0.85 (0.73-1.00	210 (4.9%)	0.57 (0.74-1.02)
WHO stage	I/II	332 (2.9%)	1.0	837 (7.8%)	1.0	731 (7.1%)	1.0
	III/IV	156 (2.1%)	1.03 (0.81-1.30)	486 (7.2%)	1.14 (0.99-1.30)	448 (6.0%)	1.00 (0.87-1.17)

TC Total Cholesterol; NRTI Nucleotide Reverse Transcriptase Inhibitors; NNRTI Non-nucleoside reverse-transcriptase inhibitors; HR Hazard Ratio; CI Confidence interval; d4T stavudine; TDF tenofovir; EFV efavirenz; NVP nevirapine

Conclusions: Older patients, those on stavudine, those overweight or with low CD4 counts should be targeted for frequent TC monitoring and identification of other risk factors of CVD in order to implement lifestyle modifications and pharmaceutical therapy.

782 Metabolic Changes and Second-Line ART in Africa (2LADY/ANRS 12169 Trial)

Amandine Cournil[1]; Assane Diouf[3]; Sabrina Eymard-Duvernay[1]; Adrien Sawadogo[2]; Liliane Ayangma[4]; Louise Fortes-Deguenonvo[3]; Jean-Marc Mben[6]; Eric Delaporte[1]; Laura Ciaffi[1]; Sinata Koulla-Shiro[5]
[1]IRD/UM 1, Montpellier, France; [2]CHU Souro Sanou, Bobo Dioulasso, Burkina Faso; [3]CRCF, Dakar, Senegal; [4]Yaounde Military Hospital, Yaounde, Cameroon; [5]FMSB/University Yaounde 1, Yaounde, Cameroon; [6]ANRS Research Center, Yaounde, Cameroon

Background: Beyond efficacy, information about the impact on metabolism of 2nd line antiretroviral combinations can be of value in the evaluation of long term benefit of treatment in the African context.

The aim was to compare changes over 48 weeks in metabolic profile of three second line regimens within the randomized 2LADY/ANRS 12169 trial (Yaounde, Cameroon; Bobo Dioulasso, Burkina Faso; Dakar, Senegal).

Methods: 451 HIV-1 positive adults, failing standard first line ART were randomized to tenofovir disoproxil fumarate (TDF) + emtricitabine (FTC) + lopinavir/ritonavir (LPV/r) [reference]; abacavir (ABC) + didanosine (ddI) + LPV/r [ABC/ddI] or TDF + FTC + darunavir (DRV) /r [DRV]. Cardiovascular disease (CVD) risk factors considered were obesity or overweight (Body Mass Index (BMI)≥25kg/m²); hypercholesterolemia (≥200mg/dL); hypertriglyceridemia (≥150mg/dL); hypertension (≥130/85mmHg) and metabolic syndrome according to IDF/AHA/NHLBI criteria.

Results: 432 (71% women) patients with a median age of 38 years were analyzed. At entry, the median CD4 count was 183 cells/µl; (IQR: 90-290), 32% were obese or overweight; and 11% had metabolic syndrome with no difference between arms.

The mean weight gain (kg) over 48 weeks was significantly greater in DRV group (+3.0±4.9) than in reference (+0.7±5.2) and in ABC/ddI groups (+0.8±4.7). In DRV group, over 48 weeks 26% of patients increased BMI from normal to overweight or obese.

In contrast, the ABC/ddI compared with DRV group had greater mean increases (mg/dL) in triglycerides (+33±68 vs -6±60; P<0.01) and in cholesterol (+30±53 vs -1±43 ; P<0.001) with significant increases in both HDL- and LDL-cholesterol. Over 48 weeks a significantly higher proportion of patients developed hypercholesterolemia, hypertriglyceridemia and metabolic syndrome in the ABC/ddI compared with DRV group. CVD risk factors did not differ between DRV and reference group.

Lipids levels changes and incidence of metabolic syndrome remained independently associated with treatment regimen in multivariable analyses including baseline clinical and metabolic variables.

Cumulative incidence at week 48	TDF+FTC+LPV/r "Reference" n = 146	ABC+ddI+LPV/r "ABC/ddI" n = 138	TDF+FTC+DRV/r "DRV" n = 148	P
Overweight/obesity	17/106 (16%)	7/84 (8%)	25/97 (26%)	<0.01
Hypercholesterolemia	27/108 (25%)	38/88 (43%)	20/99 (20%)	<0.001
Hypertriglyceridemia	18/125 (14%)	27/112 (24%)	11/125 (9%)	<0.01
Hypertension	11/112 (10%)	14/98 (14%)	13/114 (11%)	0.60
Metabolic syndrome	10/130 (8%)	18/116 (15%)	5/119 (4%)	<0.01

Both efficacy (CROI2014) and metabolic tolerance results at 48 weeks indicate that the recommended WHO regimen remains a valid option.

Conclusions: Despite a marked weight gain with high incidence of overweight and obesity in the DRV group, the most worrying changes in metabolic profile were observed in the ABC/ddI group with important increase in CVD risk factor which could compromise the long term benefit of this combination.

859 Estrogen Replacement in Healthy Postmenopausal Women Reduces %CCR5+ CD4+ T Cells

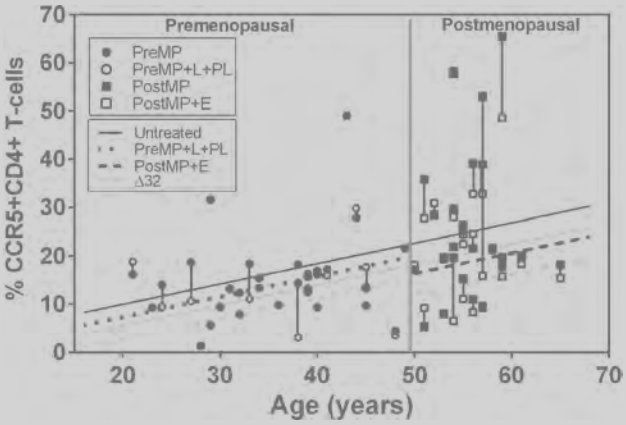
Amie Meditz[1]; Samantha MaWhinney[2]; Kerrie Moreau[2]; Kelsey Melander[2]; Joy Folkvord[2]; Wendy Kohrt[2]; Margaret Wierman[2]; Elizabeth Connick[2]

[1]Boulder Community Health, Boulder, CO, US; [2]University of Colorado Anschutz Medical Campus, Aurora, CO, US

Background: CCR5 is elevated on whole blood and cervical CD4+ T cells of healthy postmenopausal women (postMP) compared to premenopausal women (preMP), suggesting increased risk of HIV acquisition in older women. To test whether estrogen (E) downregulates CCR5, we evaluated CCR5 expression in healthy postMP who received E replacement and preMP who underwent medical induction of menopause.

Methods: Healthy HIV- women were recruited to A) 2 studies of E patch (estradiol 0.05 or 0.075 mg/day) versus placebo (PL) in postMP; B) a study of preMP who underwent menopause induction via GnRH agonist Lupron (L) with add-back E patch (0.075 mg/day) or placebo (PL); and C) an observational study of preMP. Blood was collected from preMP (early follicular phase) and postMP at baseline. Repeat sampling occurred 2 days to 4 weeks following E or PL in postMP and 4 weeks following dosing of L+E or L+PL to preMP. %CCR5+ and %CCR5+HLA-DR+CD38+ (activated) CD3+CD4+ cells were determined by flow cytometry, and CCR5Δ32 genotype by molecular analyses. Data were analyzed using mixed models and nonparametric methods.

Results: In postMP after E, %CCR5+ and %CCR5+activated cells tended to decrease (median Δ, -3.4%; p=0.16, and -5.8%; p=0.28, respectively; n=10). PostMP+PL exhibited small changes in these parameters (median Δ, -0.4%, p=0.10 and -0.8%; p=0.60, respectively; n=15). In preMP, there were statistically nonsignificant decreases after L+PL in %CCR5+ (median Δ, -0.88%, p=0.28; n=11) and %CCR5+activated cells (median Δ, -3.4%, p=0.57; n=9). PreMP who received L+E had median changes of -0.23% (p=0.82; n=9) and 7.4% (p=0.69; n=7), respectively. Across all subjects, after controlling for CCR5Δ32 genotype (p=0.29), there was a 4.2% increase in %CCR5+ (95% CI 1.5%, 6.9%; p=0.003) for every 10-year age increase (Figure). PostMP+E had 6.2% lower %CCR5+ than postMP (95% CI -10.9%, -1.6%; p=0.01). Estimated %CCR5+ tended to be lower in PreMP following L+PL (-2.7%, 95% CI -7.1%, 1.8%; p=0.23), inconsistent with the hypothesis that induction of menopause would substantially increase CCR5 expression. Similar trends were seen in %CCR5+activated cells.



Conclusions: E replacement reduces %CCR5+CD4+ T cells in healthy postMP, suggesting it could decrease HIV acquisition in this group. Lack of a sizeable increase in %CCR5+ in healthy preMP after medically induced menopause may be due to short duration of ovarian hormone suppression, unknown effects of Lupron, or different age-related effects of E on CCR5 expression.

858 CCR5 Expression in HIV-Uninfected Women Receiving Hormonal Contraception

Athe Tsibris[1]; Gaia Sciaranghella[2]; Cuiwei Wang[3]; Kerry Murphy[4]; Zaher Mehri[5]; Ruth M. Greenblatt[6]; Mardge Cohen[7]; Elizabeth Golub[8]; Heather Watts[9]; Mary A. Young[3]

[1]Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, US; [2]Ragon Institute of MIT, MGH and Harvard, Boston, MA, US; [3]Georgetown University Medical Center, Washington, DC, US; [4]Albert Einstein College of Medicine, Bronx, NY, US; [5]University of Vermont College of Medicine, Burlington, VT, US; [6]University of California San Francisco, San Francisco, CA, US; [7]Stroger Hospital and Rush University and CORE Center, Chicago, IL, US; [8]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [9]The Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US

Background: Hormonal contraception may influence a woman's susceptibility to HIV-1 infection. HIV infectivity increases as host receptor and coreceptor expression levels increase. We investigated the effect of hormonal contraception on HIV-1 receptor and coreceptor peripheral blood mononuclear cell (PBMC) expression.

Methods: We used participant samples collected from The Women's Interagency HIV Study (WIHS) between 2004 to 2011 and determined the CD4, CCR5, and CXCR4 expression levels on PBMC from HIV-uninfected women who used depot medroxyprogesterone acetate (DMPA, n=32), the levonorgestrel releasing intrauterine device (LNG-IUD, n=27), or oral contraceptive pills (OCP, n=32). Women who did not use hormonal contraception (n=33) served as a comparator group. Groups were matched by age and race and one sample per participant per group was analyzed. Our monoclonal antibody panels identified monocyte, monocytoid dendritic cell, plasmacytoid dendritic cell, $CD8^+$ T cell, and $CD4^+$ T cell subpopulations. Monocytoid and plasmacytoid dendritic cells were analyzed together as a combined dendritic cell (DC) group. We compared the proportions of cells expressing CD4 and HIV coreceptors.

Results: LNG-IUD users had an increased proportion of $CD4^+$ and $CD8^+$ T cells that expressed CCR5 (4.8 ± 0.4% and 12.5 ± 1.2%, respectively), relative to women on OCP (3.1 ± 0.3% and 8.2 ± 0.7%, $p<0.01$ and $p<0.05$) or no hormonal contraception (3.4 ± 0.3% and 7.6 ± 0.6%, $p<0.05$ and $p<0.01$). LNG-IUD use was associated with a 35% relative increase in the proportion of helper T cells that expressed CCR5 over that observed with the use of OCP and a 29% increase when compared to the use of no hormonal contraception. Increased CCR5 expression was associated with changes on central (T_{CM}) and effector memory (T_{EM}) T cells ($p<0.01$ for all comparisons). Relative increases of 6-12% in the magnitude of cellular T_{CM} and T_{EM} CCR5 expression were observed in the DMPA and LNG-IUD groups, compared to the OCP and no hormonal contraception groups ($p<0.01$ for all comparisons). No differences in the proportion of monocytes or dendritic cells that expressed CCR5, or hormone-associated changes in PBMC CD4 or CXCR4 expression levels, were detected.

Conclusions: The use of the LNG-IUD and, to a lesser extent, DMPA was associated with increased CCR5 expression on peripheral T cells. Comparative work in female reproductive tract tissues and blood is needed to further evaluate contraception-associated increases in CCR5 expression.

860 Progesterone Increases Are Associated With HIV Susceptibility Factors in Women

Alison Y. Swaims[1]; Tammy Evans-Strickfaden[1]; L Davis Lupo[1]; Alfredo Aguirre[2]; Anandi Sheth[2]; Igho Ofotokun[2]; Clyde E. Hart[1]; **Richard E. Haaland**[1]
[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]Emory University School of Medicine, Atlanta, GA, US

Background: Native progesterone and progestin-based hormonal contraception are suspected of increasing women's risk for acquiring sexually transmitted HIV. How progesterone and progestin-based contraceptives affect HIV target cells in women is uncertain. We investigated whether a population of HIV target cells in women, CD4 T lymphocytes, changes cell surface expression of the HIV CCR5 coreceptor, cell activation markers and response stimulation throughout a normal menstrual cycle.

Methods: Peripheral blood mononuclear cells (PBMCs) isolated from 7 women at 5 time points throughout their normal menstrual cycles were tested for expression of the HIV coreceptor CCR5 and the activation marker CD38 using flow cytometry. PBMCs were also stimulated *ex vivo* in the presence of Golgi transport inhibitors and intracellular production of IL-2, IFN-g and TNF-a was detected using flow cytometry. Plasma estradiol and progesterone were measured at each time point using a luminex multiplex assay. A sustained rise in plasma progesterone levels marked the beginning of the luteal phase of the menstrual cycle.

Results: The proportion of CCR5 and CD38 expressing CD4 memory T cells increased from 4% to 7% (p=0.03) from the follicular to luteal phase in 6 of 7 women. The proportion of *ex vivo* stimulated CD4 T cells with detectable intracellular TNF-a increased from 31% to 52% (p=0.006) from the follicular to the luteal phase while production of intracellular IL-2 and IFN-g remained unchanged. Increased populations of TNF-a producing cells were associated with higher plasma progesterone levels (p=0.04). The increase in TNF-a production occurred almost exclusively in cells which were also expressing IL-2 or both IL-2 and IFN-g. Time points with detectable increases in TNF-a production were the same or immediately preceding those where CCR5 and CD38 expression increased in 6 of 7 women. Estradiol levels were not associated with changes in CCR5, CD38, or *ex vivo* cytokine production.

Conclusions: Our results suggest that increases in endogenous progesterone during the luteal phase of the menstrual cycle are associated with HIV target cells that have increased expression of the HIV coreceptor CCR5, higher activation levels, and an increased response to stimulation. Knowing if these progesterone effects exist in the genital mucosa of women could be an important measure for identifying risk factors of progestin-based hormonal contraceptives.

861 Changes in Vaginal Microbiota and Cytokines in HIV-1-Seronegative Women Initiating DMPA

Alison C. Roxby[1]; David N. Fredricks[2]; Katherine Odem-Davis[1]; Kristjana H. Ásbjörnsdóttir[1]; Linnet Masese[1]; Tina L. Fiedler[2]; Walter Jaoko[3]; James N. Kiarie[3]; Julie M. Overbaugh[2]; R Scott McClelland[1]
[1]University of Washington, Seattle, WA, US; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [3]University of Nairobi, Nairobi, Kenya

Background: Depot-medroxyprogesterone acetate (DMPA) has been associated with HIV acquisition in African women. We studied changes in vaginal microbiota and inflammatory milieu after DMPA initiation, a mechanism through which DMPA may modify HIV susceptibility.

Methods: In a prospective cohort study of high-risk Kenyan women, we collected monthly vaginal swabs over 1 year pre- and post-DMPA to evaluate microbiota and immune mediators. All women initiating DMPA were included. Using quantitative PCR with specific bacterial primers, we measured quantities of *Lactobacillus crispatus, L. jensenii, L. iners*, *Gardnerella vaginalis*, and total bacterial load (16S rRNA gene levels) on vaginal swabs. Six vaginal immune mediators were measured with ELISA. Trends in detection and quantity of bacteria were estimated by logistic and linear mixed-effects regression models; cytokine trends associated with DMPA use were estimated using tobit random-effects regression.

Results: From 2010-2012, 15 HIV-seronegative women initiated DMPA, contributing 85 visits (median 6 visits/woman (range 3-8)). The median time of DMPA-exposed follow-up was 8.4 months (range 1.5-11.6). Seven women (46%) had bacterial vaginosis (BV) within 70 days before DMPA start. *L. iners* was detected in 13 women (87%) prior to DMPA start, but other lactobacilli were rarely detected. *G. vaginalis,* present in all women pre-DMPA, declined by 0.21 $\log_{10}$ copies/swab per month after DMPA exposure (p=0.011). Total vaginal bacterial load declined by 0.08 $\log_{10}$ copies/swab per month of DMPA use (p=0.017). Sustained declines in quantities of interleukin (IL)-6 (p=0.025), IL-8 (p=0.041) and IL-1 receptor antagonist (p<0.001) were noted after starting DMPA. Nine women (60%) had *L. crispatus* detected after DMPA start; *L. crispatus* detection was significantly correlated with lower levels of IL-6 and IL-8 (p=0.009, p=0.02 respectively). No decrease in BV, vaginal pH or discharge was seen after DMPA start. Declines in *G. vaginalis* and immune mediators were preserved after adjustment for sexual behavior, condom use, BV, antibiotic use and vaginal washing.

Conclusions: Initiation of DMPA led to sustained shifts in vaginal bacterial concentrations and levels of inflammatory mediators. We adjusted for likely behavioral and biological confounders, providing greater evidence that changes seen may be strongly related to DMPA. Further studies are warranted to outline specific components of the vaginal microbiota influenced by DMPA use, and the impact on HIV susceptibility.

1086 Mobile VMMC Teams in Tanzania See Older Clients and Have Higher Followup Rates

Augustino M. Hellar[1]; Dorica Boyee[1]; Hally Mahler[1]; Marya Plotkin[1]; Touma Ng'wanakilala[1]; Kelly Curran[2]; Tigistu Ashengo[2]; Hawa Mziray[1]; Erick Mlanga[3]; Sifuni Koshuma[4]
[1]Jhpiego, Dar es Salaam, United Republic of Tanzania; [2]Jhpiego, Baltimore, MD, US; [3]US Agency for International Development, Dar es Salaam, United Republic of Tanzania; [4]Ministry of Health and Social Welfare, Iringa, United Republic of Tanzania

Background: Tanzania has rolled out Voluntary Medical Male Circumcision (VMMC) since 2009 in 12 priority regions with high HIV and low male circumcision rates. More than 390,000 clients have been served in Iringa, Njombe and Tabora regions with support from Jhpiego and USAID. Nearly 80% of clients reached are aged 10-19 years. Iringa and Njombe are approaching their original 80% coverage target. Service delivery modalities include routine, in which services are delivered in larger health facilities, typically at low volume, and campaigns where teams of providers move into new communities and do 1-3 week bursts of intense, high-volume provision of services. In May 2014, mobile services were introduced specifically to serve the hard-to-reach clients not reached by other modalities. This roving team of providers, move along villages to provide VMMC services even in non-facility settings. The analysis presents findings on differences in the three modalities.

Methods: Secondary data review was conducted on 148,880 individual records, stripped-of identifiers from all three regions from October 2013-August 2014, the year when mobile teams were introduced. Records were broken into three modalities: campaign, routine and mobile. Frequencies were compared between the modalities and Chi^2 was used to test for the significance of the differences.

Results: 76% of the 148,880clients circumcised during the year were aged <20 years. Mobile teams reached older clients compared to other service delivery modalities (p<0.001), as shown below.

Overall HIV testing uptake was high (97%) regardless of the modality. A higher proportion tested HIV positive in the routine followed by mobile modalities (2.1% and 1.4% respectively). Follow-up rates were significantly higher in the mobile modality both for 1st and 2nd visits (91.7% and 63.1% respectively) compared to static modality (70% and 36% respectively); p-value < 0.001).

Service Modality	No. of clients served	% of clients < 20 years	% of Clients ≥ 20 years
Campaign	132,080	78%	22%
Routine	11,392	71%	29%
Mobile	5,408	62%	38%
Total	148,880	76%	24%

Conclusions: A higher proportion of older clients (20 years or older) accessed VMMC services through mobile teams compared to other modalities. Mobile teams are circumcising in lower volume settings than campaigns where it's easier to offer more privacy to older clients. Introduction of mobile teams could be an efficient strategy to attract older clients who have not previously accessed services. With the slightly high proportion of HIV positive clients, linkage to care and treatment must be ensured. Follow-up rates were very high in the mobile setting, probably because of active client follow-up.

1087 High Acceptability of PrePex™ Device in Routine Programmatic Settings in Rwanda

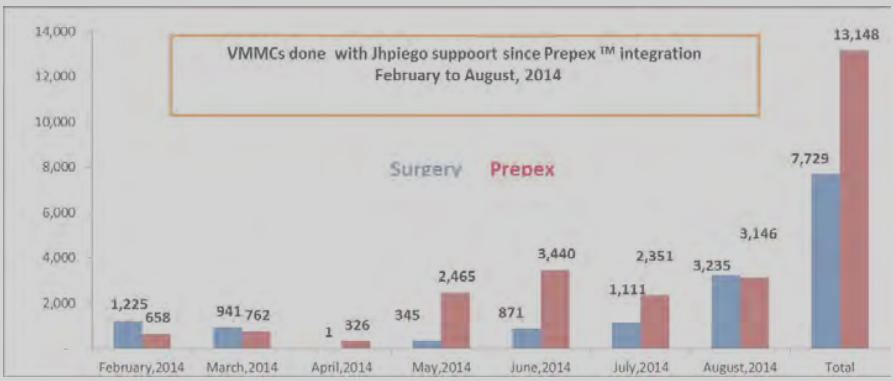
Eugene Rugwizangoga[1]; Beata Mukarugwiro[1]; Jovite Sinzahera[1]; Alphonse Mutabaruka[1]; Gloriose Abayisenga[1]; J.D. Ntakakirabose[1]; Ngeruka Leon[4]; Eugene Zimulinda[3]; Kelly Curran[2]; Tigistu Ashengo[2]

[1]Jhpiego/Rwanda, Kigali, Rwanda; [2]Jhpiego, an Affiliate of Johns Hopkins University, Washington, DC, US; [3]US Department of Defense, Rwanda, Kigali, Rwanda; [4]Rwanda Military Hospital, Kigali, Rwanda

Background: The PrePex™ device offers an alternative to conventional surgical methods of male circumcision. Because it does not require injectable anesthesia or the cutting of vital tissue, PrePex™ requires less surgical capacity and may be more acceptable to men, potentially increasing uptake of this proven HIV prevention intervention. In May 2013, PrePex™ received WHO prequalification for adults aged 18 and above. Rwanda was the first country to conduct PrePex™ safety and acceptability studies and is now the first to scale-up PrePex™ in programmatic settings. PrePex™ currently comes in five adult sizes, A through E. Since 2009, Jhpiego, with PEPFAR funding through the US Department of Defense, has supported the Rwanda Defense Force (RDF) to provide VMMC to soldiers, their dependents and civilians living near base clinics. Since February 2014 PrePex™ has been offered alongside conventional surgery to adult VMMC clients at Jhpiego-supported RDF sites.

Methods: We reviewed routine program data from Jhpiego-supported RDF sites from program inception in October 2009 through August 2014.

Results: Between October 2009 and August 2014 86,284 adolescent boys and adult men were circumcised at Jhpiego-supported RDF sites, with 20,877 of these clients served in the seven months since PrePex™ was added. Since PrePex™ was introduced nearly two thirds of circumcisions have used the device, with 13,148 (63%) of clients receiving PrePex™ and 7,729 (37%) conventional surgery. Overall uptake has been increasing year to year; the number of clients served doubled from 2012 to 2013 thanks to efficiency approaches such as task shifting to nurses and use of mobile (outreach) teams. PrePex™ introduction appears to have accelerated this trend although in July 2014 the program experienced device stockouts especially in sizes A,D and E.



PrePex™ and Surgical VMMCs Conducted at Jhpiego-supported RDF Sites, Feb-Aug 2014

Conclusions: The introduction of the PrePex™ device in routine programmatic settings is well accepted by adult VMMC clients in Rwanda, with 63% of this age group choosing PrePex™. The acceptance rate would have likely have been higher if not for a stock out of PrePex™ devices beginning in July 2014. Programs planning to scale up PrePex™ should anticipate the supply chain implications of this device which is currently available in five adult sizes.

1089 Potential Protection From HIV Transmission by Penile Cuttings in Papua New Guinea

Ivy H. Shih[1]; Lester Asugeni[2]; Matthew David[5]; Paul Horwood[5]; Parana Hewage Mangalasir[3]; David Mc Laren[3]; Rachael Tommbe[2]; Andrew Vallely[1]; Arnold Waine[4]; Stuart G. Turville[1]

[1]The Kirby Institute, Sydney, Australia; [2]Pacific Adventist University, Port Moresby, Papua New Guinea; [3]James Cook University, Cairns, Australia; [4]University of Papua New Guinea, Port Moresby, Papua New Guinea; [5]Papua New Guinea Institute of Medical Health, Goroka, Papua New Guinea

Background: Male circumcision reduces HIV acquisition by 66% but there has yet to be a scientific consensus on the protective mechanism. Current hypotheses implicate the inner foreskin due to a thinner primary barrier and greater target cell density. Unique to Papua New Guinea (PNG), ethnographic studies documented widespread non-medical penile cutting practices. The dorsal slit (DS) is the most common and leads to exposure of glans and inner foreskin and provides an opportunity to study a scenario where the inner foreskin is exposed but not removed. We present results from a cohort study assessing histological changes to thin skin that may aid prevention in both circumcised and dorsal slit men.

Methods: Foreskin samples were obtained from men with or without existing DS following elective enrolment at a free circumcision service offered at Port Moresby, PNG. Histological evaluation on frozen and paraffin embedded foreskin sections assessed primary barrier parameters that potentially afford HIV protection. Phenotypes were measured on hematoxylin and eosin stained sections: Stratum corneum thickness (SC), epithelial surface area (SA) and epithelial adhesion to the dermis, the latter two used to evaluate foreskin fragility. Alkaline expansion was conducted to representatively measure SC architecture. Imaging with a high- resolution slide scanner generated an entire tissue section image and epithelium SA was quantified with a recognition algorithm. Density and distribution of HIV target cells foreskin tissue was determined by immunofluorescence to establish foreskin vulnerability.

Results: Men with DS had significantly thicker SC in their inner foreskin than uncircumcised men: 12.09um±2.92 versus 9.87um±2.54 respectively (n=16; p<0.001; 500 total measurements). In DS individuals, the inner and outer foreskin epithelium SA collectively showed significant difference (outer: 0.0457±0.0108mm^2; inner:0.0285±0.0078mm^2) (p<0.001; 160 total measurements)). This observation was shared with epithelium-dermis adhesion (outer: 2.4583±0.7891;inner: 1.7878±0.5510) (p<0.01). CD4 T cells were also observed in the inner and outer foreskin.

Conclusions: The DS confers a degree of protection due to the inner foreskin SC thickening similar to the protective thick skin SC phenotype of outer foreskin. Beyond the protective primary barrier, the increased fragility of the inner foreskin in comparison to outer foreskin presents a new parameter that may account for the inner foreskin being a more vulnerable area.

1084 HSV-2 Shedding From Male Circumcision Wounds Among HIV-Infected Men

Mary K. Grabowski[1]; Godfrey Kigozi[2]; Ronald H. Gray[1]; Jordyn L. Manucci[3]; David Serwadda[4]; Eshan U. Patel[3]; Fred Nalugoda[2]; Maria J. Wawer[1]; Thomas C. Quinn[5]; Aaron A. Tobian[3]

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]Rakai Health Sciences Program, Kalisizo, Uganda; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]Makerere University College of Health Sciences, Kampala, Uganda; [5]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

Background: A randomized trial showed that although medical male circumcision (MMC) reduces herpes simplex virus type 2 (HSV-2) acquisition among men, MMC had no impact on HSV-2 transmission to female partners. We conducted a prospective observational study in Rakai, Uganda to assess HSV-2 shedding post-MMC.

Methods: HSV-2 shedding was evaluated among 176 HIV and HSV-2 co-infected men (145 self-reported antiretroviral therapy (ART)-naïve, 9 self-reported ART use with detectable plasma viral load (VL), and 22 self-reported ART with undetectable plasma VL of <400 copies/mL). All men underwent dorsal slit MMC. HSV-2 serostatus was determined by an HSV-2 ELISA (Kalon Biological Ltd, Guilford, UK) with positive serology defined as an optical density index value ≥ 1.5. Preoperative and weekly penile lavages for 6 weeks were tested for HSV-2 shedding and viral load using a real-time quantitative PCR assay with primers to glycoprotein B. HSV-2 shedding was defined as >50 copies of HSV-2 DNA/mL on two separate runs. Prevalence risk ratios (PRRs) and 95%CI were estimated using Poisson regression with generalized estimating equations and robust variance.

Results: HSV-2 shedding was detected in 9.7% (17/176) of men prior to MMC. There was a non-significant increase in the proportion of men with post-MMC HSV-2 shedding relative to baseline at weeks one (12.9%, 22/170, PRR=1.33, 95%CI=0.74-2.38, p=0.329) and two (14.8%, 23/155, PRR=1.50, 95%CI=0.86-2.38, p=0.153). HSV-2 shedding returned to baseline levels by week six after MMC (6.9%, 10/144, PRR=0.71, 95%CI=0.36-1.41, p=0.330). Post-operative HSV-2 shedding did not differ significantly between men who reported ART use compared to those who did not report ART use (PRR=0.67, 95%CI=0.24-1.80). HSV-2 shedding was lower among men with MMC wounds that were certified as healed (PRR=0.61, 95%CI=0.36-1.06, p=0.082). Among men with detectable HSV-2 shedding, the median HSV-2 $\log_{10}$VL/mL was elevated at week one (median=3.2, IQR=2.2-4.8) compared to baseline (median=2.3, IQR=1.8-2.9), though this difference was not statistically significant (p=0.09.) Levels of HSV-2 among men with detectable shedding were similar to baseline at all other post-operative visits.

Conclusions: Penile HSV-2 shedding was non-significantly increased during the first two weeks after MMC. Men undergoing MMC should be counseled on sexual abstinence until wound healing and consistent condom use thereafter.

1088 Self-Selection of Circumcision Acceptors, Risk Compensation and Effectiveness of Circumcision Among Service Recipients, Rakai, Uganda

Joseph Kagaayi[1]; Xiangrong Kong[2]; Godfrey Kigozi[1]; Fred Nalugoda[1]; Steven J. Reynolds[3]; David Serwadda[4]; Nelson K. Sewankambo[5]; Maria J. Wawer[2]; Ronald H. Gray[2]

[1]Rakai Health Sciences Program, Entebbe, Uganda; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, US; [4]Makerere University School of Public Health, Kampala, Uganda; [5]Makerere University College of Health Sciences, Kampala, Uganda

Background: There are limited data on characteristics of acceptors of safe male circumcision (SMC), risk compensation and effectiveness of SMC service programs. We compared baseline characteristics of SMC acceptors and non-acceptors, determined the effectiveness of SMC and compared trends in sexual behaviors of the two groups using data on men aged 15-49 years enrolled in the Rakai community cohort study in Uganda.

Methods: 1192 non-Muslim HIV-negative SMC acceptors were compared to a stratified random sample of 2384 uncircumcised men. Baseline behaviors and trends over time were compared using multivariable modified Poisson with generalized estimating equations. HIV incidence rates between the groups were compared using the incidence rate ratio (IRR) from a multivariable Poisson regression model.

Results: Overall SMC acceptors were younger, less likely to be currently or previously married, and had higher education attainment. Among sexually active men, baseline sexual behaviors were comparable between the groups. However SMC acceptors had 26 percent higher prevalence of genital ulcers compared to non-acceptors (p=0.025). After circumcision, the rate of increase in prevalence of sexual activity was 2.6 percent higher among SMC acceptors (p<0.001) compared to non-acceptors. On stratification by age, the difference was 3.2 percent higher, p=0.08 among youths (15-24) but no difference was seen above 24 years. The prevalence of sexual activity with women in higher risk occupations (bar attendants, alcohol brewers, restaurant workers, itinerant traders, fisher folk, housemaids), increased by 10.2 percent per year among SMC acceptors (p=0.007) but no change occurred among uncircumcised men. Trends in other sexual behaviors were similar between the groups. HIV incidence among SMC acceptors was 0.61/100 person years and 1.11/ 100 person years among non-acceptors (adj. IRR=0.50, p=0.05, 95 percent CI=0.25-1.01).

Conclusions: The higher prevalence of genital ulcers among sexually active SMC acceptors suggests that higher risk sexually active men self-selected to receive SMC. The suggestion of faster increase in sexual activity among circumcised youths and the increase in partnerships with higher risk women suggest possible behavioral disinhibition and need to be investigated in other settings. Though these behaviors, did not attenuate the effectiveness of SMC, there is need to add avoidance of high risk partners to the current SMC messaging.

Session O-5 Oral Abstracts — Room 613

4:00 pm – 6:00 pm

NeuroAIDS Pathogenesis and Antiretroviral Therapy

56 Randomized Clinical Trial of Antiretroviral Therapy for Prevention of HAND

Fujie Zhang[1]; Robert Heaton[2]; Hao Wu[3]; Hua Jin[2]; Hongxin Zhao[4]; Xin Yu[5]; Donald Franklin[2]; Weiwei Mu[1]; Florin Vaida[2]; **Scott Letendre**[2]

[1]Chinese Center for Disease Control and Prevention, Beijing, China; [2]University of California San Diego (UCSD), San Diego, CA, US; [3]Capital Medical University, Beijing You'an Hospital, Beijing, China; [4]Capital Medical University Beijing Ditan Hospital, Beijing, China; [5]Peking University, Beijing, China

Background: Neurocognitive (NC) impairment (NCI) is common among treated HIV+ adults and can occur for several reasons, including production of viral proteins in the CNS, neuroinflammation, and antiretroviral therapy (ART) neurotoxicity. To date, clinical trials have focused on treatment of existing NCI and have been largely inconclusive. We conducted a clinical trial to determine whether one ART regimen would better prevent NCI than another.

Methods: 250 HIV+, ART-naive adults were randomized to either open-label zidovudine-lamivudine-nevirapine (ZLN) or tenofovir-lamivudine-efavirenz (TLE) at two hospitals in Beijing. All subjects were NC normal and had CD4+ T-cell counts below 350/mm^3 at entry. Subjects were followed for 96 weeks with comprehensive NC testing and safety assessments. NC performance was adjusted for local normative data and summarized by the Global Deficit Score (GDS) and by the proportion of subjects who developed incident NCI. NC change was summarized using a regression-based summary change score (SCS). Intent-to-treat completer (ITT-C, n=239) and as-treated (AT, n=189) analyses were performed.

Results: The treatment groups had similar demographic and disease characteristics, including plasma HIV RNA (mean 4.2 $\log_{10}$ copies(c)/mL in both groups) and CD4+ T-cell counts (mean 235.1 (ZLN) vs. 222.1 (TLE), p=0.32). GDS values at entry were also similar (mean 0.12 (ZLN) vs. 0.14 (TLE), p=0.15). A high proportion of subjects attained virologic suppression: 92% had plasma HIV RNA below 50 c/mL in both groups at 48 weeks (p=.65, ITT-C). TLE was associated with greater risk of incident NCI over 96 weeks than ZLN in either ITT-C (p=.009) or AT (p=0.037) analyses. Consistent with this finding, the SCS also differed between the groups at 96 weeks (ITT-C: d=.27, p=0.016; AT: d=.28, p=0.034). Safety assessments identified that 73/128 (57.0%) subjects in the ZLN group had at least one adverse event compared with 42/122 (34.4%) in the TLE group, leading to greater discontinuation of study drugs in the ZLN group (38% vs. 2%, p<.001). The most common adverse events were liver toxicity and bone marrow suppression.

Conclusions: This is the first randomized clinical trial to demonstrate that ART regimens differ in preventing NC decline using comprehensive NC testing. Possible explanations include differences between the regimens in drug distribution into the CNS and neurotoxicity. The substantial difference in other adverse events dictates additional research to identify a less toxic alternative to ZLN.

57 Neurocognitive Function in Africans Failing First-Line ART and Responses to Second Line

Andrew D. Kambugu[1]; Jennifer Thompson[2]; James Hakim[6]; Dinah Tumukunde[10]; Joep van Oosterhout[7]; Anne Hoppe[2]; Charles Kwobah[9]; Sarah Walker[2]; Nicholas Paton[8]
On behalf of the EARNEST Trial Team

[1]Infectious Diseases Institute, Makerere University Kampala, Kampala, Uganda; [2]University College London, London, United Kingdom; [3]Joint Clinical research Centre, Kampala, Uganda; [4]Queen Elizabeth Central Hospital, Malawi, Blantyre, Malawi; [5]AMPATH, Kenya, Eldoret, Kenya; [6]University of Zimbabwe, Harare, Zimbabwe; [7]Dignitas International, Zomba, Malawi; [8]National University of Singapore, Singapore, Singapore; [9]Moi University College of Health Sciences, Eldoret, Kenya; [10]Joint Clinical Research Centre, Kampala, Uganda

Background: Neurocognitive impairment is an important co-morbidity in HIV infection. Data describing neurocognitive function in patients from sub-Saharan Africa are generally sparse, with only limited data describing neurocognitive function at the time of failure of first-line therapy, and none describing the changes in neurocognitive function in response to second-line therapy.

Methods: We studied patients who were enrolled in EARNEST, a large multi-centre trial of second-line therapy conducted at 14 sites in sub-Saharan Africa. Eligible patients were >12 years old and failing first-line therapy according to WHO criteria after >12 months on an NNRTI-based regimen. Patients were randomised to take second-line therapy (open-label) with lopinavir/ritonavir (400mg/100mg twice daily) plus either 2-3 clinician-selected NRTIs, raltegravir, or as monotherapy after 12 weeks' induction with raltegravir. Neurocognitive function was tested on those aged >18 years at baseline (switch to second-line), weeks 48 and 96 using colour trails tests 1 and 2, and the grooved pegboard test. Test results were converted to a composite z-score using US test norms.

Results: 1036 patients (>86% of those >18 y enrolled in the trial) had evaluable tests at baseline, and 915 patients at week 96. Patients were 58% female, mean age 38 years, median viral load 65,000 c/ml, median CD4 count 73 cells/mm3 at first-line failure. Mean (SD) composite z-score at baseline was -2.96 ± 1.74; z-scores were independently lower in older individuals, and those with lower body weight, higher viral load, lower haemoglobin, fewer years of education, fewer working hours per week, previous CNS disease, or taking fluconazole (all P<0.05 in a multivariable model). Neurocognitive function improved markedly after starting second-line therapy (mean (SE) increase in Z-score of +1.23 (0.04) at week 96), with no difference between the arms (P=0.35; Figure 1).

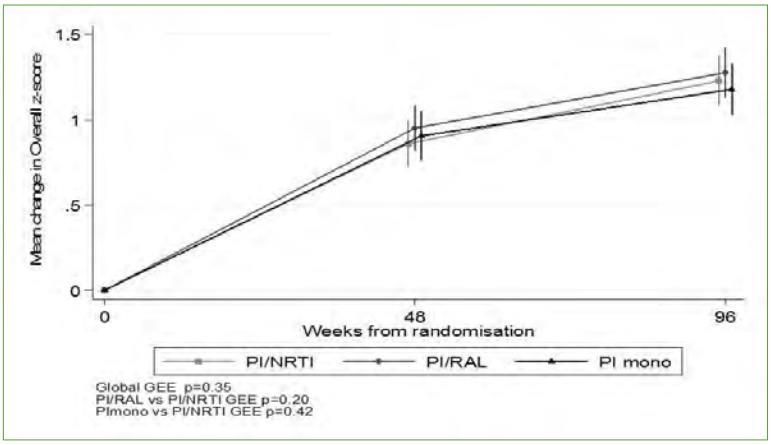


Figure 1: Changes in z-score over 96 weeks in the three randomised groups

Conclusions: Patients in sub-Saharan Africa failing first-line therapy appear to have severely impaired neurocognitive function. In part this may reflect inadequate data for normalization, but the relationship with high viral load and indicators of general debility suggest much of the impairment is HIV-related. Neurocognitive function improves markedly on second-line therapy. The lack of difference between standardised treatment regimens with very different CNS penetration indicates that this need not be a primary consideration in the choice of an optimal drug regimen for second-line therapy.

58 Compartmentalized HIV Rebound in the CNS After ART Interruption

Sara Gianella Weibel; Michelli Faria de Oliveira; Konrad Scheffler; Matt Strain; Antonio De la Torre; Scott Letendre; David M. Smith; Sergei L. Kosakovsky Pond; Ronald J. Ellis
University of California San Diego, La Jolla, CA, US

Background: If strategies currently in development succeed in eradicating HIV reservoirs in peripheral blood and lymphoid tissues, residual sources of virus may remain in anatomic compartments, including the central nervous system (CNS). To design effective eradication strategies, it is crucial to determine to what extent compartmentalized HIV reservoirs contribute to viral rebound after antiretroviral therapy (ART) interruption

Methods: Paired blood and cerebrospinal fluid (CSF) samples were collected from 14 chronically HIV-infected individuals undergoing ART interruption. At the first two available time-points following viral rebound, we sequenced HIV-1 *env* (*C2-V3*), *gag (p24),* and *pol (*reverse transcriptase) regions amplified from cell-free HIV RNA in blood and CSF using

the Roche 454 FLX Titanium platform. Analyses of viral genetic compartmentalization and evolution in CNS and blood were used to identify the likely source compartment (blood or CSF, with the latter representing the CNS anatomical compartment) of HIV RNA rebound following ART interruption. At the same time-points, we measured levels of different soluble markers of inflammation and cellular trafficking (i.e. soluble [s]CD14, sCD163, IL-2, IL-6, IL-8, TNF-α, IL-10, MCP-1 and MIP-1α in blood and CSF).

Results: In ten out of 14 participants viral rebound populations were compartmentalized between blood and CSF (F_{st}, $p \leq 0.05$ for at least one gene). Seven participants were sampled within three weeks of the first detectable HIV RNA in CSF, suggesting that rebound originated within CNS rather than migrating from blood. At the second sampled time-point, three additional participants became compartmentalized. Only one participant remained panmictic (genetically mixed populations) for the entire study follow-up. Levels of four cytokines (IL-2, IL-6, sCD163 in blood and TNF-α in CSF) were higher in non-compartmentalized participants ($p \leq 0.05$), but none was significant after adjusting for multiple testing.

Conclusions: Our study suggests that HIV reservoirs in the CNS contribute to viral rebound in most HIV-infected subjects interrupting ART. Reservoirs in all anatomic compartments need to be actively targeted to achieve a complete functional cure.

59 Impaired Blood-Brain Barrier Integrity Is Associated With Neuronal Injury in HIV

Birgitta Anesten[1]; Lars Hagberg[1]; Henrik Zetterberg[2]; Staffan Nilsson[3]; Bruce J. Brew[4]; Dietmar Fuchs[5]; Richard Price[6]; Magnus Gisslén[1]

[1]University of Gothenburg, Gothenburg, Sweden; [2]University of Gothenburg, Gothenburg, Sweden; [3]Mathematical Sciences, Chalmers University of Technology, Gothenburg, Sweden, Gothenburg, Sweden; [4]University of New South Wales, Sydney, Australia; [5]Division of Biological Chemistry, Biocenter, Medical University, Innsbruck, Austria, Inssbruck, Austria; [6]University of California San Francisco, San Francisco, CA, US

Background: Blood-brain barrier (BBB) damage is prevalent in HIV. The aim of this study was to assess the prevalence of BBB disruption in different stages of HIV-infection and study risk factors and potential association with neuronal injury.

Methods: Using a cross-sectional design and archived CSF samples from three cohorts (Gothenburg, Sweden; San Francisco, USA; Sydney, Australia), we compared BBB integrity (CSF/plasma albumin ratio) with CSF and blood concentrations of HIV RNA and neopterin, CSF WBC count, and CSF neurofilament light protein (NFL) in 7 HIV-infected groups (n=657): 4 groups of untreated 'neuroasymtpomatic' (NA) subjects defined by blood CD4+ T cells of >350, 200-349, 50-199, and <50 cells/μL; 2 groups of untreated patients with HIV-associated dementia (HAD) staged by severity (stage 1 vs 2-4); subjects on antiretroviral treatment (ART) with P HIV-RNA <50 copies/mL >6 months. An HIV-uninfected control group was also examined (n=53).

Results: The albumin ratio was significantly increased in HAD as compared to all other groups with highest levels in those with more severe dementia. 68 % of patients with HAD had increased albumin ratio compared to 16 % of NA subjects without ART. No significant difference in albumin ratio was found between NA untreated subjects, subjects on ART, and HIV-negative controls. Significant correlations between BBB integrity and CSF WBC count ($p<0.01$, $r_s=0.16$), CSF HIV RNA levels ($p<0.01$, $r_s=0.14$), blood ($r_s=0.20$) and CSF ($r_s=0.25$) neopterin, and age ($r_s=0.24$; all $p<0.001$) were found in NA untreated subjects. In a multiple linear regression analysis only age and CSF neopterin stood out as independent predictors to albumin ratio with adjusted estimates in the multivariate analysis. Furthermore, a significant correlation was found between albumin ratios and CSF NFL concentrations in untreated patients ($p<0.001$, $r_s=0.40$) as wells as in patients on ART ($p<0.001$, $r_s=0.57$). Albumin ratio was confirmed as an independent predictor of CSF NFL together with age, CD4 and CSF WBC count.

Conclusions: BBB disruption is mainly found in patients with HAD. Neither untreated neuroasymtpomatic subjects, nor patients on antiretroviral treatment had albumin ratios that were significantly different from HIV-negative controls. Intrathecal immunoactivation is a risk factor of BBB impairment and the association with CSF NFL suggest a pathogenic pathway between inflammation, BBB disruption and neural injury before development of dementia.

60 Cortical and Subcortical Brain Volumes in Primary HIV Infection

Patrick W. Wright[1]; Ashmit Pyakurel[3]; Kevin Robertson[4]; Julia Peterson[5]; Henrik Zetterberg[7]; Dietmar Fuchs[6]; Richard Price[5]; Dieter Meyerhoff[5]; Serena Spudich[2]; Beau Ances[1]

[1]Washington University School of Medicine, Saint Louis, MO, US; [2]Yale University School of Medicine, New Haven, CT, US; [3]Louisiana Tech University, Ruston, LA, US; [4]University of North Carolina, Chapel Hill, NC, US; [5]University of California San Francisco, San Francisco, CA, US; [6]Innsbruck Medical University, Innsbruck, Austria; [7]University of Gothenburg, Gothenburg, Sweden

Background: HIV enters the nervous system soon after seroconversion. Though effects of chronic HIV infection on volumes of cortical and subcortical brain regions are well characterized, little is known about the extent of volumetric alterations that may occur within the first year of infection. We assessed brain volumes in antiretroviral therapy (ART)-naïve subjects with primary HIV infection (PHI, <1 year after initial infection) and age-matched HIV-uninfected participants (HIV-). We correlated volumes with neuropsychological performance (NP), blood, and cerebrospinal fluid (CSF) biomarkers to examine mechanisms of and clinical associations with regional brain volumes during PHI.

Methods: CSF, blood, NP testing, and structural T1 magnetic resonance imaging scans were acquired from 18 HIV- and 48 PHI male participants. Volumetric measurements were obtained (using Freesurfer 5.1) from the following regions of interest (ROIs): caudate, amygdala, corpus callosum, ventricles, putamen, thalamus, cortical white matter, and total grey matter. Student's t-test assessed volumetric differences in these ROIs between the two groups. Pearson correlations examined relationships during PHI between volumetric measures and biomarkers in CSF [viral load (VL), neopterin, and neurofilament light-chain (NFL)], and blood (VL, CD4+, and CD8+ T cell count), and NP tests [digit-symbol (DSST), grooved pegboard (GPD), finger-tapping (FT), and timed gait (TG)].

Results: PHI (median 106 days after estimated infection) and HIV- participants were similar in age (36.7 and 35.2 years, respectively) and education (16.1 years and 15.42 years). Only the putamen was significantly different (decreased volume) in PHI compared to HIV- ($p=0.05$). Within the PHI group, putamen volume associated directly with decreasing CD4+ count ($p=0.004$, Fig. 1A). Trends for inverse correlations were noted for CSF/plasma albumin ratio ($p=0.07$) and CSF NFL ($p=0.09$). Reductions in putamen volume in PHI participants were associated with worse performance on the DSST ($p=0.05$), FT ($p=0.05$), and TG ($p=0.02$, Fig. 1B) tests.

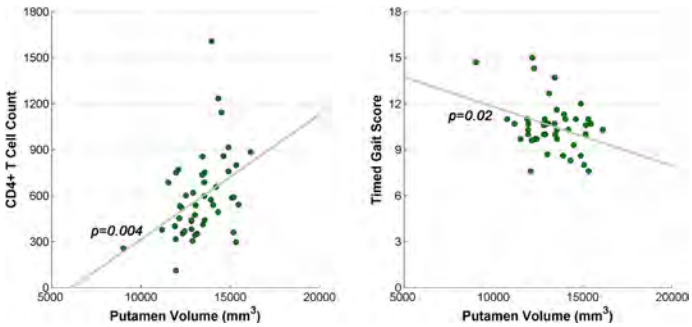


Figure 1. In primary HIV infection, the volume of the putamen (in cubic milimeters) is significantly positively correlated with CD4+ T cell count (A) and inversely associated with decreasing performance on the timed gait neuropsychological task (B).

Conclusions: Our volumetric results suggest that the putamen may be specifically affected in the first year of HIV infection, and the volume of this structure associates with systemic immune measures and neurocognitive performance during this period. Longitudinal analyses are required to assess whether early introduction of ART might stabilize or reverse these structural changes observed in PHI.

61 IRF4 Transcription Factor Associated With Integrated HIV DNA in Brain Macrophages

Benjamin B. Gelman[1]; Joshua G. Lisinicchia[1]; Tetyana P. Buzhdygan[1]; Vipulkumar Patel[1]; Tyler Clement[1]; Samantha A. Trevino[1]; Kristofer R. Jennings[1]; Dennis L. Kolson[2]

[1]University of Texas Medical Branch, Galveston, TX, US; [2]University of Pennsylvania, Philadelphia, PA, US

Background: Integrated HIV DNA (HIV_{int}) can become transcriptionally silenced and latently expressed in certain types of resting lymphocytes. In the brain viral infection occurs predominantly in macrophage type cells in which viral latency is not as thoroughly investigated. To identify the cellular targets of eradication therapy in the CNS we compared macrophage markers in human brain specimens containing high and low concentrations of latent HIV DNA.

Methods: Integrated HIV DNA, total HIV DNA and HIV RNA were measured in frontal neocortex from 40 patients using qPCR or the O'Doherty two-step Alu-Gag assay. Infected patients were separated into those with less than or greater than 3% HIV_{int} relative to the number of HIV RNA copies. Macrophage-expressed mRNAs were measured using qPCR in these groups and a group of 21 seronegative controls. Differences were evaluated with one-way ANOVA and Tukey tests.

Results: High and low HIV_{int} groups had equivalent HIV RNA copies per gram of brain tissue. The group with high HIV_{int} had significantly greater expression interferon regulatory factor 4 (*IRF4*) ($p < 0.03$). mRNAs corresponding to macrophage and microglial type marker antigens CD163, CD14, CD16, Mac387 and Iba-1 were not significantly different. IRF4 protein expression in specimens with higher HIV DNA was localized histologically in brain M2 macrophages preferentially and often was co-localized with low Zeste 2 and high JMJD3, which are two critical elements of the Polycomb Repressor Complex (PRC).

Conclusions: High macrophage *IRF4* mRNA expression is associated with a higher concentration integrated HIV DNA in the brain. IRF4 is a nuclear transcription factor involved in active macrophage polarization towards M2 phenotypes. It is regulated epigenetically by the PRC. The results suggest that HIV-infected macrophages undergoing active polarization toward M2 phenotypes via IRF4 expression contribute disproportionately to the establishment of the latent pool of integrated HIV DNA in the brain.

62 Longitudinal Assessment of Blood Brain Barrier Disruption in Primary HIV Infection

Elham Rahimy[1]; Fang-yong Li[2]; Alex Russell[4]; Julia Peterson[4]; Lars Hagberg[3]; Henrik Zetterberg[3]; Richard Price[4]; Magnus Gisslén[3]; Serena Spudich[1]

[1]Yale University School of Medicine, New Haven, CT, US; [2]Yale Center for Analytical Sciences, Yale University, New Haven, CT, US; [3]University of Gothenburg, Gothenburg, Sweden; [4]University of California San Francisco, San Francisco, CA, US

Background: Abnormal blood brain barrier (BBB) permeability has been implicated in the neuropathogenesis of chronic HIV infection. As neurocognitive impairment can persist despite effective combination antiretroviral therapy (cART), it is possible that irreversible CNS processes are initiated in early infection. We analyzed the natural history of BBB permeability in primary HIV infection (PHI), as well as the effects of cART initiated during this period.

Methods: Blood and CSF were collected from 108 cART-naive participants with PHI (94% male, median age=36, days post-transmission, dpt=91) at baseline and in follow-up visits. 57 of the 108 subjects initiated cART during follow-up for reasons independent of the study. BBB permeability was evaluated as CSF:Serum albumin ratio (QAlb). Baseline log_{10}QAlb was compared with 39 uninfected age-matched control subjects (82% male, median age=38). The mixed-effects model was used to analyze longitudinal change of log_{10}QAlb post transmission, adjusting for baseline age. Longitudinal association between log_{10}QAlb and the axonal injury marker neurofilament light chain (NFL) was examined with between-subject correlation and within-subject correlation.

Results: At baseline, PHI subjects demonstrated elevated median log_{10}QAlb compared to age-matched uninfected controls (0.721 vs. 0.635, p=0.002). Over a median follow-up of 475 dpt in the PHI cohort (median visits=3.0), log_{10}QAlb demonstrated a nearly flat trajectory (slope=-4.9E-5, p=0.532). 23 PHI participants with baseline QAlb greater than previously reported age-specific upper limits of normal (ULN) demonstrated statistically significant yet modest decreases in log_{10}QAlb over time (slope=-0.0017, p=0.013). Levels of those with baseline below the ULN did not change (slope=-7.9E-5, p=0.004). Log_{10}QAlb did not significantly change over time after cART initiated at a median 225 dpt (slope=1.39E-4, p=0.255; median 398 days of treatment, median 2 visits). Log_{10}QAlb correlated with log_{10}NFL as determined by within-subject (r=0.543, p=0.001) and between-subject (r=0.469, p<0.001) correlations.

Conclusions: BBB permeability remains elevated during the course of early HIV infection and does not demonstrate measurable improvement over a year of follow up after cART initiation. Additionally, QAlb was longitudinally associated with increased expression of the neuronal injury biomarker NFL. HIV-associated neuropathogenesis may be initiated and maintained early in the course of infection, and continue despite effective cART.

63 Declining Prevalence of HIV-Associated Neurocognitive Disorders in More Recent Years

Carmela Pinnetti; Raffaella Libertone; Pietro Balestra; Patrizia Lorenzini; Martina Ricottini; Samanta Menichetti; Maria Maddalena Plazzi; Mauro Zaccarelli; Adriana Ammassari; Andrea Antinori

National Institute for Infectious Diseases, Lazzaro Spallanzani, Rome, Italy

Background: Overall prevalence of neurocognitive impairment (NCI) has been estimated as high even in the cART era. More recently, lower NCI prevalence has been found in MSM, suggesting that it may be previously overestimated. Aim of the study was to evaluate prevalence of HIV-associated neurocognitive disorders (HAND) and predictive factors in more recent years of cART impact.

Methods: Single-centre, retrospective, cross-sectional analysis of neurocognitive profile in HIV-infected cART-treated patients. All patients underwent neuropsychological assessment (NPA) by standardized battery of 14 tests on 5 different domains. People were classified as having HAND according to Frascati's criteria. Chi-square for trend, and multivariable logistic regression were fitted.

Results: 569 consecutive HIV-infected cART-treated individuals from 2009 to 2014, contributing a total of 858 NPA tests, were included (male 82%; median age 48 years; MSMs 51%; HCV+ 15%; CD4 nadir >200 cell/ mm^3 61%; current CD4 >350 cell/mm^3 83%; HIV-RNA <40 c/mL 83%). At the time of NPA, 49% of patients were receiving a NNRTI-based, 32% a PIr-based, and 11% a NRTI-sparing regimen, for a median time of exposure to current regimen of 25 months (IQR 9-46). A cognitive complaint of memory loss, attention deficit or concentration difficulties was observed in 313 (36%) tested patients, whereas 545 (64%) were non-complaining. HAND prevalence was 48% in complaining (ANI=23%; MND=21%; HAD=4%) and 16% in non-complaining patients (ANI=12%; MND=4%; HAD=0). By calendar periods, prevalence of HAND in complaining was 50% in 2009/2010, 45% in 2011/2012 and 48% in 2013-2014 (P at chi square for trend=0.74). In non-complaining was 20%, 22% and 9%, respectively (P at chi square for trend=0.004). Factors associated to HAND by multivariable logistic regression are reported in Table.

Table. Factors predictive of HAND by multivariable logistic regression

	Complaining (n=313)			Non-complaining (n=545)		
Factors	OR	95%CI	P	OR	95%CI	P
Age (per 10 years increase)	1.29	0.87-1.72	0.078			
Nadir CD4 - 0-199 - >=200				1.00 0.57	0.33-1.00	0.051
CD4 at NPA - 0-349 - >=350	1.00 0.43	0.24-0.76	0.004			
Years of infection				1.08	1.04-1.12	<0.001
Education (per yr more)	0.82	0.76-0.88	<0.001	0.84	0.78-0.90	<0.001
HCV-coinfection	1.87	0.94-3.69	0.072			
NNRTI-based PIr-based NRTI-sparing	1.00 1.07 0.30	0.58-1.96 0.11-0.81	0.83 0.018	1.00 0.99 0.42	0.54-1.80 0.17-1.09	0.97 0.075

Multivariable models were adjusted for variables with p<0.1 at univariable analysis. The model for complaining was adjusted also for mode of HIV transmission, CDC stage and the model for non-complaining for age and CD4 at NPA.

Conclusions: In very late cART era, in a prevalent MSM population, HAND prevalence was close to 50% only in patients selected to NPA for a cognitive complaint. In people with no specific cognitive complaints, prevalence of HAND was confirmed as lower than previously detected, estimated as less than 10% in the more recent years. Higher CD4 count at NPA, higher CD4 nadir, a shorter time from HIV diagnosis and higher educational level were associated to a lower risk of NCI. Receiving a NRTI-sparing ART at cognitive assessment seems to be related to a lower risk of impaired cognition.

Session S-1 Symposium — Room 6C

4:00 pm – 6:00 pm

Harnessing Antibodies for Prevention and Therapeutics

64 Potentiating Protective Antibody Activity: A Systems Serology Approach

Margaret E. Ackerman

Thayer School of Engineering, Dartmouth College, Hanover, NH, US

Antibodies act as a nexus between innate and adaptive immunity: they provide a means to engage a spectrum of innate immune effector cells in order to clear viral particles and infected cells. This functional landscape is remarkably complex, as the humoral response is highly polyclonal, with multiple antibody variants directed to multiple epitopes on multiple viral antigens, and diversity of viral recognition characteristics is further complemented by diversity in ability to recruit the potent anti-viral effector functions of a suite of innate immune effector cells. In vivo, even neutralizing antibodies rely on this ability to act as molecular beacons for innate immunity in order to provide protection, and results from both human and macaque studies have implicated these effector functions in vaccine-mediated protection. We demonstrate a high-throughput, high-content platform for the biophysical and functional interrogation of the innate immune recruiting capacity of polyclonal HIV-specific antibodies capable of parsing this complex humoral milieu into components that can be used to develop computational models of antibody activity and provide insights into mechanisms of vaccination.

65 Impact of Repetitive Protein Boosting on RV305 HIV-1 Vaccine-Induced Antibodies

Georgia D. Tomaras

Duke University Medical Center, Durham, NC, US

Of the six HIV-1 vaccine efficacy trials to date, only one trial, RV144, demonstrated decreased transmission *versus* the placebo group, with an estimated vaccine efficacy of 60% and 31% at 12 and 42 months, respectively. Antibodies that significantly correlated with HIV-1 infection risk included IgG (in particular IgG3) non-broadly neutralizing antibodies (non-bnAbs) to the V1/V2 region of HIV-1 envelope glycoprotein. Although not broadly neutralizing, these antibodies could mediate antibody Fc-mediated antiviral functions, such as antibody dependent cellular cytotoxicity (ADCC).

A unique feature of the RV144 vaccine regimen was the inclusion of a protein boost that was antigenic for both linear strain-specific V2 antibodies, as well as for conformational V1V2-glycan epitopes bound by broad neutralizing antibodies (bnAbs). A subset of RV144 vaccinees were boosted, after a 6-8 year interval, as part of the RV305 vaccine trial. This repetitive boosting with the vaccine immunogen both expanded a pool of antibodies with many of the characteristics of V1V2 bnAbs and, as well, skewed the plasma IgG subclass profile associated with non-bnAbs. New technologies have allowed a deeper interrogation of the B cell repertoire post vaccination and provide insights on the quest to induce broadly neutralizing antibodies and / or further drive non-bnAbs with Fc-mediated antiviral functions.

Coauthors: M. Anthony Moody[1], David Easterhoff[1], LaTonya Williams[1], Kevin Saunders[1], Nicole Yates[1], Nicos Karasavvas[4], Sheetal Sawant[1], Nathan Vandergrift[1], Judith Lucas[1], Robert Howington[1], Jerome Kim[2], Nelson Michael[2], Merlin Robb[2], Robert O'Connell[4], Sandhya Vasan[4], Jean-Louis Excler[2], Supachai Rerks-Ngarm[3], Punnee Pitisuttithum, Sorachai Nitayaphan[4], Thomas Kepler[5], Munir Alam[1], Guido Ferrari[1], David Montefiori[1], Hua-Xin Liao[1], and Barton Haynes[1]

[1]Duke Human Vaccine Institute, Duke University, Durham, NC 27710; [2]MHRP; [3]Thai Ministry of Health; [4]AFRIMS; [5]Boston University

66 Immunoprophylaxis by Gene Transfer: Shortcut to an HIV Vaccine

Phil Johnson

Children's Hospital of Philadelphia, Philiadlphia, PA, US

The holy grail of HIV vaccine development is an immunogen that elicits antibodies which neutralize field strains of HIV from multiple clades. However, little progress has been made in generating such vaccine candidates, and near-term prospects remain uncertain. In the meantime, we have taken a different approach to HIV immunoprophylaxis that completely bypasses the adaptive immune response. The concept is straightforward. One selects an antibody (or antibody-like molecule) with the desired neutralizing properties, clones the respective gene, and then inserts it into a recombinant adeno-associated virus (rAAV) vector. When injected (intramuscularly) into a host, the vector directs *in vivo* production of the antibody that leads to serum neutralizing activity against HIV. In other words, antibodies are produced by myofibers instead of plasma cells. We adapted this

approach for the SIV model system and engineered sterilizing immunity in monkeys against a virulent SIV challenge virus. Importantly, antibody levels in "immunized" monkeys have been stable for over 6 years. We have now moved this concept into Phase 1 human clinical trials.

67 Broadly Neutralizing Antibodies for HIV-1 Eradication Strategies

Dan H. Barouch

Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US

We have previously shown that the broadly neutralizing monoclonal antibody PGT121 afforded substantial therapeutic efficacy in viremic, chronically SHIV-SF162P3-infected rhesus monkeys. In a recent study, we have also explored the efficacy of PGT121 in ART-suppressed, SHIV-SF162P3-infected monkeys. In addition, we recently observed that the viral reservoir is established very early following infection and prior to viremia. These data demonstrate new challenges facing HIV-1 eradication strategies and suggest novel approaches to target the viral reservoir.

Session S-2 Symposium — Room 6D

4:00 pm – 6:00 pm

Current Issues in HIV-Related Malignancies

68 HIV-Associated Malignancies: The Worldwide Epidemic

James J. Goedert

National Cancer Institute, Bethesda, MD, US

Background: Malignancies in people with HIV are a major cause of morbidity and mortality. With improving control of HIV infection, the burden and complexities of malignancies are increasing.

Methods: Recent publications and public data were reviewed, focusing on international patterns and differences between AIDS-defining cancers (ADC) and non-ADC.

Results: In the USA, the incidence and burden (total number of cases) of malignancies fell dramatically from 1993-1998, but this was exclusively ADC, specifically Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL). Since 1998, age-adjusted incidence has been stable while burden of non-ADC has increased. From 2012-2015, ADC incidence increased 5-10% outside North America and Europe. Southern and especially east Africa continue to have the highest burden of KS. Cervix cancer has had the highest incidence and burden especially in Africa, but most cases do not have HIV. Aging is increasing the importance of ADC, the most important of which are cancers of the lung, anus and liver. Lung cancer is by far the most common ADC, but incidence fell from 1996-2010, perhaps due to smoking reduction. Anus and liver cancers are increasing, probably due to longer survival with HPV and HCV, respectively. Hodgkin lymphoma is decreasing, probably with better control of HIV. Mortality due to NADC has been increasing in most populations.

Conclusions: Implementation of programs to address malignancies are needed, especially in low and middle-income countries. Global access and use of effective antiretroviral therapy is paramount, but research is needed to integrate and optimize combined antiretroviral and cancer therapies. Reducing the burden of cervix and anus cancers will require global access and use of HPV vaccines, but VIA with simplified HPV screening could be a useful interim approach. Liver cancer burden would be reduced with broader use of HBV vaccine and HCV direct-acting agents. Smoking cessation is needed to reduce the morbidity and mortality from lung cancer and many other diseases.

69 Viral Oncogenesis: Evolving Concepts

Shannon C. Kenney

University of Wisconsin, Madison, WI, US

AIDS-related malignancies are often associated with oncogenic viruses, in particular Epstein-Barr virus (EBV) and Kaposi Sarcoma herpesvirus (KSHV). This lecture will discuss how viruses contribute to AIDS-related cancers (with particular emphasis on EBV), and describe novel virus-targeted therapies.

70 AIDS Lymphoma: Advances and Existing Challenges

Ariela Noy

Memorial Sloan Kettering Cancer Center, New York, NY, US

Despite dramatic advances in anti-retroviral therapy, HIV related lymphoma remains a challenge. Lymphoma is the largest contributor to cancer deaths among HIV infected persons and accounts for about 10% of all deaths. Though the incidence has changed, HIV infected person with good CD4 counts still have a marked increase risk of lymphoma with the exception of primary central nervous system lymphoma Gibson et al. (AIDS 2014) have recently estimated an 11 fold increase overall and 17 fold increase for AIDS defining subtypes. These authors also note an increased risk for lymphomas not previously associated with HIV.

71 HIV Malignancies in Low- and Middle-Income Countries: A Double Burden of Disease

Jackson Orem

Uganda Cancer Institute, Kampala, Uganda

One of the hallmarks of AIDS has been the elevated risk of developing cancers linked to immunosuppression. The introduction of highly active antiretroviral therapy (HAART) has greatly changed the natural history of HIV infection and associated morbidities. In Western countries the cumulative risk of developing and dying from AIDS defining cancers (ADCs) such as Kaposi's sarcoma, non-Hodgkin's lymphoma (NHL) and invasive cervical cancer, has significantly declined. On the other hand, non-AIDS-defining cancers (NADCs), such as hepatocellular carcinoma, anal cancer, lung cancer significantly increased.

Cancers therefore still represent a significant burden of HIV-associated morbidity in the current era of HAART worldwide. Few studies have highlighted clearly the impact of scale up of HAART on cancer burden in resource-limited settings such as in Sub-Saharan Africa. It is prudent to state that the highest burden of HIV and cancers are currently found in these countries. It is ironic that in practice linkage between HIV and cancers at this point in LMIC is based on extrapolation from the developed world experience. This has probably contributed to the challenges being faced in translating this model for intervention in LMIC. The resources available and background cancer risks factors in these two settings are diametrical at best.

By and large, the epidemiology of malignancies in the developing world are driven by infectious agents mainly viruses such Human Herpes virus 8(HHV8), Epstein Barr Virus (EBV), human papilloma virus (HPV) infection and hepatitis B and C (HBV and HCV). The observations from these countries still show that the cancers common in HIV-infected individual are very much reminiscent of the era before wide spread use of HAART; given the magnitude of AIDS-defining cancers such as Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer.

There is therefore need to better understand the impact of HAART optimization on cancer burden and picture in LMIC. In doing this there must be tools and means for assessing the potential impact of optimized care in LMIC. This may include implementation of interventions that incorporate strategies for both ADC and NADC. Research aimed at understanding local situation but also answering global questions on HIV and cancers at this point can best be done in LMIC. The critical requirement for this undertaking in LMIC must emphasize infrastructure and human capacity development in these countries.

Session S-3 Symposium **Room 6AB**

4:00 pm – 6:00 pm

Current Imperatives in HIV Prevention and Treatment

72 How Has HIV Prevention Affected the Spread of Other Sexually Transmitted Infections?

Marie Laga

Institute of Tropical Medicine, Antwerp, Belgium

At the start of the HIV epidemic in the early 80's, rates of other STI were high among MSM, SW and even general population in many parts of the world. Because AIDS was deadly without cure at the time, attention to primary prevention resulted in sexual behavior change including more condom use. During the late 80thies and 90thies, STI prevalence rates declined substantially. When ART became available and later, evidence emerged that ART can also prevent HIV transmission, the epidemiology of STI changed again. Among MSM in Western countries for example, rates of classic STI (syphilis, gonorrhea) increased since early 2000, and outbreaks of "old" STI (LGV) or "new" STI (Hepatitis C) were described. The possible role of the different HIV prevention strategies on the patterns of STI in different populations will be analyzed and discussed in this presentation.

73 HIV Risks and Vulnerabilities Among Gay Men and Other Men Who Have Sex With Men Across Sub-Saharan Africa

Stefan Baral

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

In the context of the generalized HIV epidemics across Sub-Saharan Africa, it is often proposed that key populations with specific HIV acquisition and transmission risk factors are less relevant because HIV transmission is sustained among reproductive age adults with average HIV acquisition and transmission risks. While some countries in Western and Northern Africa have concentrated epidemics, the continental countries in Southern and Eastern Africa all have generalized epidemics, a categorization independent of the burden of disease among key poplations including gay men and other men who have sex men (MSM). However, the past decade has witnessed an improved understanding of both the presence of communities of gay men and other MSM across Sub-Saharan as well as their HIV-related risks and vulnerabilities.

Where there are data among MSM, they suggest a complex mixture of individual level, network level, and structural risks for both the acquisition and transmission of HIV. Together, these risks manifest in high prevalence, and where measured, high HIV incidence among young men who have sex with men. Moreover, where phylogenetic data are available characterizing HIV transmission clusters, they often suggest overlap of the circulating strains among MSM with those among other reproductive age men and women. Moreover, there are complex structural determinants of HIV risks including widespread social stigma manifesting in fear of seeking health care, targeted violence, and further criminalization of same-sex practices and even homosexuality as a sexual orientation. These social constructs often result in a data paradox where we know the least about the HIV-risks and vulnerabilities in the places with the most stigma.

Moving forward necessitates a combined effort of academia, community, government, and implementing partners. Improved epidemiologic inputs to inform better mathematical models characterizing population attributable fraction are crucial given the limited investment into the HIV-related needs of these men. Concurrently, adding HIV prevention and treatment options combined with enhanced implementation to improve coverage of existing and future programs is important in changing the trajectory of these HIV epidemics. Lastly, building the evidence base of the adverse public health consequences associated with widespread stigma and increasingly punitive legal contexts may facilitate successful advocacy for the changing of these laws by local champions.

74 An Expanded Behavioral Paradigm for Treatment and Prevention of HIV-1

Thomas J. Coates

University of California Los Angeles, Los Angeles, CA, US

This presentation will address the social and behavioral priorities for prevention and treatment of HIV-1 infection. The approach presented will be based on the premises that (1) Social and behavioral strategies are necessary and essential, but not sufficient for preventing and treating HIV-1 infection; (2) The major advances in prevention and treatment of other infectious and chronic diseases have come about through policy, legislative, and systemic interventions, rather than those focused only on the individual; and (3) The social and behavioral agenda needs to include all of the behaviors (testing, access to care, maintenance in care, adherence to treatment) in comprehensive intervnetions that also include the organization of many actors and systems essential in facilitating prevention or improving treatment. Social and behavioral strategies for achieving high coverage, acceptability, and effectiveness will be presented.

75 Social Protection, Financial Incentives, and Prevention of HIV

David Wilson

World Bank, Washington, DC, US

Background: Social protection may be defined as public actions to reduce extreme poverty and vulnerability. Cash transfers (CTs) are an important and growing element of social protection and may be conditional (CCTs) which are contingent on specified actions or behaviors or unconditional (UCTs) which are not contigent.

A review of the literature identified over 50 randomized controlled trials (RCTs) evaluating the effects of RCTs on education, health and income, including sexually transmitted infections (STIs) and HIV.

Three World Bank RCTs with biomarker endpoints show that cash transfers reduce STI and HIV infection. In Tanzania, people offered up to $60 each annually to stay STI-free had 25 percent lower STI prevalence (De Walque et al 2012). In Malawi, girls and parents offered up to $15 monthly to stay in school had 60% lower HIV prevalence - whether they stayed in school or not (Ozler et al, 2012). In Lesotho, adolescents offered a lottery ticket to win up to $50 or $100 every four months if they stayed STI and HIV-free had a 25% lower HIV incidence - 33% lower among girls and 31% in the $100 arm (De Walque et al 2012).

Discussion: These studies are promising, but have methodological challenges. Tanzania and Malawi used STI and HIV prevalence, respectively. Two NIH HPTN studies reporting soon will provide decisive evidence. Questions to be answered include: (i) is the evidence robust enough? (2) Are cash transfers scalable and sustainable? (3) How durable are the effects, after cash transfers end? (4) Are there opportunities to combine cash transfers with other proven interventions, such as PrEP among the highest risk populations, including key populations and young women in hotspots in hyper-endemic countries?

Special Session: Ebola Virus Disease: Responding to the Challenge

76 The Médecins Sans Frontières Experience with the Current Ebola Outbreaks

Gilles Van Cutsem

Médecins Sans Frontières, Mowbray, Cape Town, South Africa

In December 2013 a two year old child in the village of Meliandou in the southern Guinean forest was infected with the Ebola virus, most likely acquired from a bat. This single zoonotic transmission event has led to the largest Ebola virus disease outbreak in history, which has killed more than 8,000 and infected more than 22,000 people in Guinea, Liberia and Sierra Leone. More than 800 health care workers have been infected; more than 500 have died. As a consequence, the extremely fragile health systems of West Africa almost came to a standstill, resulting in morbidity and mortality of other diseases adding to that of Ebola. Yet most of the response has been carried by West African health workers and communities, while the international response was slow and uncoordinated.

Since March 2014 Médecins Sans Frontières (MSF), in partnership with Ministries of Health, has admitted more than 7,700 patients, among whom nearly 5000 were confirmed with Ebola. MSF provides care in 8 Ebola Case Management Centres and two transit centres, with approximately 650 beds, and has over 300 international and 3800 national staff on the ground in January 2015. Last year, 28 MSF staff members were infected with Ebola, the vast majority in the community; 14 have died. More than 1,400 tonnes of supplies have been shipped. MSF's strategy to control Ebola is organised into six elements: isolation and supportive medical care for cases, including laboratory capacity to confirm infection; safe burial activities; awareness raising; alert and surveillance in the community; contact tracing; and access to healthcare for non-Ebola patients, including protection of health facilities and health workers. These activities are interdependent and all must be in place to contain the epidemic.

As was demonstrated in previous outbreaks as well as recently in the D.R.C., Mali, Nigeria, Norway, Senegal, Spain, the U.K. and the U.S., Ebola outbreaks can be controlled early on by rapid and vigorous outbreak control measures. Yet, the world was unable to contain this epidemic. This presentation will present challenges and lessons learned by MSF during the first year of the response. Incidence has decreased recently yet many challenges remain unaddressed. MSF has called repeatedly on the international community to provide a strong, flexible, and coordinated response, with limited success. The first lesson we must retain is that thousands have died because of international negligence.

77 Ebola Treatment and Vaccine Development and Implementation: Challenges and Opportunities

H. Clifford Lane

National Institute of Allergy and Infectious Diseases, Bethesda, MD, US

WEDNESDAY, FEBRUARY 25, 2015

Session PL-1 Plenary **4AB Auditorium**

8:30 am – 9:00 am

Preventing Pediatric HIV and Managing HIV-Infected Children: Where Are We Now and Where Are We Going?

78 Preventing Pediatric HIV and Managing HIV-Infected Children: Where Are We Now, and Where Are We Going?

Diana M. Gibb

University College London, London, United Kingdom

By 2015, the MDGs and 'Double Dividend' Initiatives aimed for 'virtual' global elimination of perinatal HIV. 2015 also marks 30 years since ACTG 076 trial showed MTCT reduction with AZT; new paediatric HIV is now rare in rich countries. However, globally, 240,000 children acquired HIV in 2015; >90% live in 22 high-burden countries, 21 in Africa. WHO 2013 guidelines recommended 'Option B' pMTCT (endorsed by recent results from the PROMISE trial) or 'Option B+' (ART for life, in high fertility/high HIV countries; now adopted by 15 countries). With pMTCT expansion, new child infections have fallen by ~50% since 2007. Option B+ is also aiding ART rollout to lower-level clinics but challenges of retention on postnatal ART, partner testing and concerns about bone safety of tenofovir for exposed children need further research. Infant HIV diagnosis remains a major challenge; in 2013, <45% exposed infants had DNAPCR by age 2months. More importantly, as >90% HIV-infected children will be born to undiagnosed mothers or those not on ART and 50% children die by their 2nd birthday, a shift is urgently needed to early clinical recognition, HIV diagnosis, and ART with cotrimoxazole prophylaxis initiated locally, alongside pMTCT/treatment for adults. Early infant ART reduced mortality 4-fold in the CHER trial; over >5 years, even ART for 1 or 2 years was superior to delayed ART. Pragmatically, WHO 2013 guidelines recommend ART for children <5years, extended to <15yrs in some countries; recent data suggest this may improve pubertal development and long-term immunological health. By 2013, 760,000 children worldwide had started ART; however, coverage for those needing ART was only 24% (36% in adults), emphasizing need for integration with MCH services and ART harmonization with adults, where possible. Paediatric solid-based combination ARTs are available, dosed by weight bands backed by African data, and as daily regimens (eg 3TC/ABC+EFV). Children respond very well to ART, with few side-effects and even after perinatal ART exposure. Daily dolutegravir for 1st/2nd-line ART is promising, will be evaluated in the planned ODYSSEY trial and may allow better future harmonisation with adults and across paediatric weight bands. With ART, children are reaching young adulthood; global cohort study collaboration through an IAS initiative is focused on adolescent outcomes and linkage of paediatric/adult cohorts; this is vital to study long-term effects of early childhood HIV/ART.

Session PL-2 Plenary **4AB Auditorium**

9:00 am – 9:30 am

Directing Chronic Virus Infection Through Viral Regulation of Innate Immune Defenses

79 Directing Chronic Virus Infection Through Viral Regulation of Innate Immune Defenses

Michael Gale

University of Washington, Center for Innate Immunity and Immune Disease, Seattle, WA, US

Innate immune defenses are essential for restricting virus replication and spread, and for programming the adaptive immune response for protection against infection. Our studies have revealed key features of innate immunity, starting with nonself discrimination for identification of virus infection, to innate immune effector genes and responses that serve to restrict viral replication and spread. Studies of hepatitis C virus (HCV), a heptotropic RNA virus, have identified RIG-I-like receptors (RLR) signaling of interferon regulatory factor (IRF)3 activation as a critical event initiating the innate immune response to infection from within the host cell. This process propagates through induction of innate immune effectors genes, including type 1 and 3 interferons and interferon stimulated genes (ISGs). ISG products include antiviral factors that restrict virus replication, and proinflammatory cytokines and chemokines that facilitate innate immune cell activation and lymphocyte response toward the infected liver. HCV disrupts these process through the actions of the

viral NS3/4A protease that cleaves MAVS, a key adaptor protein in the RLR pathway, resulting in loss of IRF3 activation and target gene expression, thus supporting viral persistence. Comparison of innate immune signaling outcomes within cells infected with HCV or HIV defines viral regulation of IRF3, and suppression of ISG products, as shared feature of chronic virus infection. Our studies reveal specific nodes of the innate immune response that are subject to viral and host control, and whose actions impart control over the progression of acute to chronic infection transition. Targeting innate immune actions of the host should be formally considered in therapeutic strategies to interrupt persistence for clearance of chronic virus infection.

Session O-6 Oral Abstracts — Room 615

10:00 am – 12:00 pm

Intracellular and Clinical Pharmacology, Drug Interactions, and Adherence

80 Scientific Overview: The Clinical Pharmacology of HIV Prevention

Marta Boffito

Chelsea and Westminster Hospital, NHS Foundation Trust/Imperial College, London, United Kingdom

The combination of tenofovir and emtricitabine is the only PrEP agent that was studied and showed efficacy in preventing HIV transmission, and its pharmacology in this context has been studied in depth. However, prospective randomized clinical trials have reported varying efficacy due to poor adherence to the drug. Importantly, this could be overcome by the introduction of long-acting injectable PrEP agents which may be administered monthly and ensure optimal and prolonged drug exposure in HIV target tissues. Pharmacological studies in the setting of HIV PrEP are fundamental to inform on different drug pharmacokinetics, pharmacodynamics and pharmacogenetics in view of the absence of easily measurable surrogate markers of efficacy, as they play a central role in interpreting drug concentration–responses and optimal drug exposure achievement. Existing strategies for the prevention of HIV infection and ways in which pharmacology may be a valuable resource for understanding drug pharmacokinetics, determining pharmacodynamic targets, identifying optimal drug combinations/doses, frequency of dosing, and designing clinical trials will be discussed.

81 Intracellular Pharmacokinetics of Sofosbuvir In Vivo

Joseph Rower[1]; Ariel Hodara[1]; Jacob A. Langness[3]; Sarah Tise[1]; Greg Everson[1]; Aimee Truesdale[2]; Fafa Baouchi-Mokrane[2]; Lane Bushman[1]; Peter L. Anderson[1]; Jennifer J. Kiser[1]

[1]University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, US; [2]Denver Health and Hospital Authority, Denver, CO, US; [3]University of Colorado Health, Aurora, CO, US; [4]University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, US

Background: Sofosbuvir (SOF), an inhibitor of the Hepatitis C virus (HCV) NS5B polymerase, is a uridine nucleotide analog pro-drug. In cells, SOF is metabolized by host enzymes to GS-331007 (007) mono- (MP), di- (DP), and the pharmacologically active tri-phosphate (TP). There are limited data on the pharmacology of 007 TP in various cell types. We sought to characterize the pharmacology of SOF in peripheral blood mononuclear cells (PBMC).

Methods: PBMC were collected from HCV-infected individuals receiving SOF-based HCV treatment during routine clinic visits. HCV treatment duration was extracted from medical records and times of prior doses were by patient self-report. 007 MP, DP, and TP concentrations were determined using a validated LC-MS/MS assay linear in the range of 50-50000 fmol/sample, then normalized to a concentration per 10^6 cells (fmol/M). Log transformed data were naïve pooled to calculate 007 MP, DP and TP half-lives ($t_{1/2}$). Effects of clinical covariates on 007 phosphate concentrations were tested using unpaired t-tests for categorical covariates or Pearson correlation for continuous covariates.

Results: PBMC were obtained from 45 individuals (29 genotype 1, 28 male, 5 African-American, 31 cirrhotic, 22 decompensated) receiving SOF plus ribavirin (RBV, n=27), simeprevir (SIM, n=7), or both (n=11) for a median (range) of 29 (19, 162) days of treatment and between 2.3 and 27 hours post-dose. All TP samples were quantifiable, while 2 MP and 16 DP were below the limit of assay detection. Median (range) concentrations were 220 (51.5, 846), 70.2 (25.8, 275), and 859 (54.5, 6756) fmol/M for PBMC 007 MP, DP, and TP, respectively. Estimates of $t_{1/2}$ were 13.8 (MP) and 26.0 (TP) hours. MP (203 vs. 375 fmol/M; p=0.03) and TP (970 vs. 2280 fmol/M; p=0.01) were significantly higher in subjects taking SIM. 007 phosphate concentrations did not differ by race, sex, presence of cirrhosis or decompensation and were not significantly correlated with age, weight or creatinine clearance.

Conclusions: 007 phosphates are formed within PBMC, with the TP moiety representing the major anabolite. Higher MP than DP concentrations suggest that DP production may be a rate limiting step. 007 TP was predicted to have a long intracellular half-life in PBMC. SIM co-administration was associated with higher 007 MP and TP, possibly due P-glycoprotein inhibition by SIM. Additional well-controlled pharmacokinetic studies of intracellular SOF are needed, including an assessment of cell-specific pharmacology.

82 Drug-Drug Interactions Between Anti-HCV Regimen Ledipasvir/Sofosbuvir and Antiretrovirals

Polina German; Kimberly Garrison; Phillip S. Pang; Luisa M. Stamm; Adrian S. Ray; Gong Shen; Marc Buacharern; Anita Mathias

Gilead Sciences, Inc., Foster City, CA, US

Background: Use of some anti-HCV agents with antiretrovirals (ARVs) in coinfected patients may be complicated by drug-drug interactions (DDIs). A fixed-dose combination tablet composed of the NS5A inhibitor ledipasvir (LDV) 90 mg and NS5B inhibitor sofosbuvir (SOF) 400 mg is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults. We conducted a Phase 1 study to evaluate the potential DDI between LDV/SOF and protease-inhibitor (PI)-containing ARV regimens: ritonavir [RTV, r] boosted atazanavir (ATV/r) or darunavir (DRV/r) plus emtricitabine/tenofovir DF (FTC/TDF; TVD).

Methods: This was a multiple-dose, randomized, cross-over study in healthy volunteers. In Part A (simultaneous dosing), subjects received LDV/SOF, ARVs (Cohort [CH] 1: ATV/r (300 mg/100 mg)+TVD (200 mg/300 mg); CH 2: DRV/r (800 mg/100 mg)+TVD), and LDV/SOF+ARVs each for 10 days. In Part B (CH 3 and CH4), an evaluation of staggered (12 hour) dosing of LDV/SOF and ARVs was conducted.

LDV, SOF, GS-331007 (predominant circulating metabolite of SOF), and ARV plasma concentrations were analyzed and PK parameters were calculated. 90% CIs for the geometric least squares means ratios (%; combination vs. alone) for analytes' AUC_{tau}, C_{max} and C_{tau} were estimated by a linear mixed effect model and compared to lack of PK alteration boundaries of 70-143%. Safety assessments were conducted during the study.

Results: Ninety-five of 96 subjects (N=24/CH) completed the study; one CH 2 subject withdrew consent. Most adverse events (AEs) were Grade 1 or 2. Most commonly reported AEs were ocular icterus with ATV (22%, N=21; CH 1 and 3), headache (19%, N=18; all CH), and nausea (18%, N=17; all CH). One SAE of abdominal pain (Grade 3) was concluded related to ATV/r+TVD by the investigator.

Modest increases in LDV and GS-331007 with ATV/r+TVD and a small reduction in SOF with DRV/r+TVD were observed. Increases in ATV and RTV were also observed, and TFV exposures were elevated with both ARV regimens, following either simultaneous or staggered administration of LDV/SOF.

Pharmacokinetic Results

Change in PK Parameter	Simultaneous				12-Hour Stagger			
	Effect of LDV/SOF on ARVs							
	ATV/RTV+TVD+ LDV/SOF vs. ATV/RTV+TVD							
	ATV	RTV	FTC	TFV	ATV	RTV	FTC	TFV
AUC_{tau}	↔	↔	↔	↔	↑43%	↔	↔	↔
C_{max}	↔	↔	↔	↑47%	↔	↔	↔	↑46%
C_{tau}	↑63%	↑45%	↔	↑47%	↑108%	↑70%	↔	↑38%
	DRV/RTV+TVD + LDV/SOF vs. DRV/RTV +TVD							
	DRV	RTV	FTC	TFV	DRV	RTV	FTC	TFV
AUC_{tau}	↔	↔	↔	↑50%	↔	↔	↔	↑38%
C_{max}	↔	↔	↔	↑64%	↔	↔	↔	↑46%
C_{tau}	↔	↑48%	↔	↑59%	↔	↔	↔	↑52%
	Effect of ARVs on LDV/SOF					
	ATV/RTV+TVD+LDV/SOF vs. LDV/SOF					
	LDV	SOF	GS-331007	LDV	SOF	GS-331007
AUC_{tau}	↑96%	↔	↔	↑134%	↔	↑50%
C_{max}	↑68%	↔	↔	↑75%	↔	↔
C_{tau}	↑118%	NA	↑42%	↑164%	NA	↔
	DRV/RTV+TVD+ LDV/SOF vs. LDV/SOF					
	LDV	SOF	GS-331007	LDV	SOF	GS-331007
AUC_{tau}	↔	↓27%	↔	↔	↓37%	↔
C_{max}	↔	↓37%	↔	↔	↓31%	↔
C_{tau}	↔	NA	↔	↔	NA	↔

Note: 90% CI of the GLSM ratio were within (↔), extended above (↑), or extended below (↓) the predetermined lack of PK alteration boundaries of 70% to 143%; NA: not estimated

Conclusions: Study treatments were generally well tolerated. LDV/SOF increases TFV exposure within RTV-boosted ATV- or DRV-based regimens. The safety of higher TFV concentrations in this setting has not been established. Consider alternative HCV or ARV therapy to avoid increases in TFV. Patients should be monitored for TFV-associated adverse reactions if coadministered.

83 Emtricitabine-Triphosphate in Dried Blood Spots (DBS) as a Marker of Recent Dosing

Jose R. Castillo-Mancilla[1]; Lane R. Bushman[1]; Amie Meditz[2]; Sharon M. Seifert[1]; Jia-Hua Zheng[1]; L Anthony Guida[1]; Edward M. Gardner[3]; David V. Glidden[4]; Robert M. Grant[4]; Peter L. Anderson[1]

[1]University of Colorado-AMC, Aurora, CO, US; [2]Beacon Center for Infectious Diseases, Boulder, CO, US; [3]Denver Health and Hospital Authority, Denver, CO, US; [4]University of California San Francisco, San Francisco, CA, US

Background: Tenofovir diphosphate (TFV-DP) in red blood cells (measured in DBS) is a strong marker of cumulative adherence to tenofovir disoproxil fumarate/emtricitabine (TDF-FTC) and highly predictive of PrEP efficacy. However, because of its long half-life, TFV-DP does not discriminate recent vs. remote dosing. FTC is phosphorylated to FTC-triphosphate (FTC-TP) in red blood cells, which is simultaneously measured with TFV-DP in DBS, but the half-life and clinical utility of FTC-TP have not been elucidated. We aimed to determine the half-life of FTC-TP in DBS and to evaluate its utility as a marker of recent dosing.

Methods: DBS were collected from 13 HIV-negative and 10 HIV-infected adults participating in an intensive pharmacokinetic (PK) study of daily TDF-FTC for 30 days in HIV-negative individuals and 60 days in HIV-infected subjects. DBS were obtained following dosing on days 1, 3, 7, 20, 30 and 60 in all participants and also on days 35 and 45 (off drug) in the HIV-negative group. FTC-TP was extracted from a 3mm punch and quantified using LC-MS/MS with a lower limit of quantification (LLOQ) of 0.1 pmol/punch. Plasma TFV-FTC was quantified using LC-MS/MS with a LLOQ of 10 ng/ml. The FTC-TP half-life was determined using one-compartment first-order PK. To assess the effectiveness of FTC-TP as a marker of recent dosing, the concordance of FTC-TP in DBS with TFV-FTC in plasma was determined by comparing paired plasma/DBS samples collected at various study visits from participants receiving daily TDF-FTC in the iPrEx Open Label Extension (iPrEx OLE). Data are presented as median (range).

Results: Following dosing, FTC-TP reached Cmax at 4 (2-8) hours and exhibited a half-life of 31 (22-52) hours, with no difference according to HIV status (p=0.43). The FTC-TP average concentration at steady state was 0.25 (0.16-0.37) pmol/punch. A total of 482/515 (94%) paired plasma/DBS samples from iPrEX OLE were concordant for detection/non-detection of TFV/FTC in plasma vs. FTC-TP in DBS. When TFV/FTC were BLQ in plasma, FTC-TP was BLQ in DBS 98% of the time. When TFV/FTC were quantifiable in plasma, FTC-TP was quantifiable in DBS 90% of the time.

Conclusions: FTC-TP has a 31 hour half-life in DBS (compared with 17 days for TFV-DP). Excellent concordance (94%) was observed between detection of FTC-TP in DBS with detection of TFV/FTC in plasma, demonstrating that FTC-TP informs recent TFV/FTC dosing, thereby complimenting the long-term cumulative adherence measure provided by TFV-DP.

84 Impact of EFV PK/PG on Neuropsychological Performance in Older HIV+ Patients

Uriel S. Sandkovsky[1]; Anthony T. Podany[1]; Courtney Fletcher[1]; Andrew Owen[2]; Angela Felton-Coleman[1]; Kevin Robertson[3]; Susan Swindells[1]

[1]University of Nebraska Medical Center, Omaha, NE, US; [2]University of Liverpool, Liverpool, United Kingdom; [3]University of North Carolina, Chapel Hill, NC, US

Background: Despite being one of the most commonly prescribed first line antiretroviral agents, the pharmacokinetics (PK) and pharmacodynamics of efavirenz (EFV) and its 8-hydroxy metabolite (8-OH-EFV), have not been robustlyrobustly evaluated in older HIV-infected patients. Moreover, 8-OH-EFV has been shown to be more neurotoxic in vitro than EFV. We sought to investigate relationships between neuropsychological performance (NP) with EFV and 8-OH-EFV PK in HIV-infected individuals >50 yo.

Methods: Cross sectional study of HIV-infected adults >50 yo, on EFV containing ART > 12 weeks. 12 h and 18 h post-dose plasma EFV and 8-OH-EFV were quantified via LC-MS-MS. *CYP2B6* polymorphisms were investigated. NP battery assessed executive function, motor skills, verbal learning, memory, and speed of processing, CES-D depression scale and sleep quality index questionnaire were completed. Correlations of EFV and 8-OH-EFV plasma concentrations with NP performance, sleep, depression scores and *CYP2B6* polymorphisms were assessed (Spearman's correlation, and univariate logistic regression where appropriate).

Results: 30 participants 24 men, 6 women with mean age 57 yrs (50-68)were enrolled. Mean CD4 was 736/mm^3 (range 145-2062); 26 participants had HIV RNA <20 c/mL and 4 < 100 c/mL. Median 12h and 18h EFV plasma concentrations were 1967 ng/mL (IQR 1476-2394) and 1676 ng/mL (IQR 1120-2062) respectively. Median 12hr and 18hr 8OH-EFV plasma concentrations were 378 ng/mL (IQR 223-589) and 384 ng/mL (IQR 216-621) respectively. EFV plasma concentrations did not correlate significantly with NP performance. Higher 8-OH-EFV plasma concentrations correlated with better learning (p=0.002), language (p=0.002) and total NPZ scores (p=0.005). Neither EFV nor 8OH-EFV plasma concentrations

correlated with sleep disturbance or depression. The *CYP2B6* 516G>T polymorphism was associated with significantly higher concentrations of EFV at 12h and 18 h (p=0.02) but not NP function.

Conclusions: Better neurocognitive functioning was associated with higher 8-OH EFV but not EFV plasma concentrations. No correlation was observed with disturbed sleep or depression and exposure to EFV or the metabolite. These findings point to a need for greater understanding of the metabolic profile of EFV and 8-OH EFV in plasma and the CNS and relationships with antiviral effect and neurotoxicity.

85LB Levonorgestrel Implant + EFV-Based ART: Unintended Pregnancies and Associated PK Data

Kimberly K. Scarsi[1]; Kristin M. Darin[3]; Shadia Nakalema[2]; David Back[4]; Pauline Byakika-Kibwika[2]; Laura Else[4]; Sujan Dilly-Penchala[4]; Susan Cohn[3]; Concepta Merry[5]; Mohammed Lamorde[2]

[1]University of Nebraska Medical Center, Omaha, NE, US; [2]Infectious Diseases Institute, Kampala, Uganda; [3]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [4]University of Liverpool, Liverpool, United Kingdom; [5]Trinity College Dublin, Dublin, Ireland

Background: The subdermal levonorgestrel (LNG) implant is recommended for long-acting, reversible contraception with high efficacy (expected failure rate <1%). Efavirenz (EFV)-based antiretroviral therapy (ART) may decrease LNG pharmacokinetic (PK) exposure via cytochrome P450 mediated drug-interactions. A priori, we hypothesized that over 1 year of combined use, EFV would reduce LNG exposure, but not below the proposed threshold for contraceptive efficacy (180 pg/mL).

Methods: We present the final, 48-week results of a longitudinal, parallel group, PK evaluation of HIV-infected, Ugandan women desiring an implant for contraception. A standard dose LNG implant was inserted at entry in two groups: (1) subjects not yet eligible for ART (control group; n=17); (2) subjects with undetectable HIV-RNA on tenofovir/emtricitabine/efavirenz (EFV group; n=20). At each visit, subjects were counseled on condom use and a pregnancy test was performed. Blood was collected at 1, 4, 12, 24, 36, and 48 weeks after entry and plasma LNG concentrations were analyzed by a validated LC-MS/MS method, with an assay calibration range of 50-1500 pg/mL. Demographic data were analyzed with a T-test or chi-square, as appropriate. PK data were reported as geometric means (GM) and GM ratio.

Results: All women were Black African with a mean age of 31 years. Subjects in the EFV group were on EFV for a median of 10 (range 5-66) months prior to entry. PK data are presented in the Table and reveal a 45-57% reduction in LNG concentrations beginning at week 1 and persisting through week 48. Unexpectedly, 3 women in the EFV group became pregnant between weeks 36 and 48. No pregnancy occurred in the control group. The LNG concentration prior to pregnancy in each subject was 122, 297, and 303 pg/mL, measured 2, 8, and 2 weeks, respectively, prior to conception. For subject safety, the EFV study arm was halted. At the last study visit, 15 subjects (75%) in the EFV group, but no subjects in the control group, had LNG concentrations below 303 pg/mL (the highest concentration at which a pregnancy was observed; p<0.001).

LNG plasma concentrations over 48 weeks

Week	Control group (n=17)	EFV group (n=20)	EFV:Control GM ratio
1	1070 (783, 1356)	462 (370, 553)	0.43 (0.41, 0.47)
4	667 (541, 792)	359 (280, 437)	0.54 (0.52, 0.55)
12	590 (475, 704)	327 (268, 385)	0.55 (0.55, 0.56)
24	528 (423, 633)	280 (212, 348)	0.53 (0.50, 0.55)
36	618 (520, 716)	279 (149, 409)	0.45 (0.29, 0.57)
48	580 (477, 684)	247* (209, 285)	0.43 (0.42, 0.44)

Data presented as pg/mL and geometric mean (GM) with 90% confidence intervals, unless indicated.

* n=11; excludes 3 pregnant patients and 6 subjects who did not reach the week 48 endpoint due to study arm closure.

Conclusions: Contraceptive failures (15%) were seen among HIV-infected women on EFV-based ART within a year of receiving an LNG implant, and LNG exposure was markedly reduced. In addition, the proposed threshold for LNG efficacy (180 pg/mL) was inadequate in our study population. Alternative contraception should be offered to women on EFV-based ART plus LNG implant, but studies of novel implant dosing strategies should be pursued.

86LB A Phase IV PrEP Study Reveals Limited Ex Vivo Potency of Oral Maraviroc Against HIV-1

Julie Fox[1]; Carolina Herrera[2]; Juan Manuel Tiraboschi[1]; Akil Jackson[3]; Laura Else[4]; Natalia Olejniczak[2]; Saye Khoo[4]; David Back[4]; Robin Shattock[2]; Marta Boffito[3]
On behalf of KCL Infectious Diseases Biobank

[1]Guys and St Thomas' NHS Foundation Trust, London, United Kingdom; [2]Imperial College London, London, United Kingdom; [3]Chelsea and Westminster Hospital, NHS Foundation Trust, London, United Kingdom; [4]University of Liverpool, Liverpool, United Kingdom

Background: Oral pre-exposure prophylaxis (PrEP) may be an effective prevention strategy against HIV-1 transmission. All completed PrEP clinical trials have tested ARV acting post-viral entry in the target cell. We present results of the first PrEP study evaluating the potential of an entry inhibitor, maraviroc, in a phase IV, multi-site, open-label, randomized controlled pharmacokinetic and *ex vivo* pharmacodynamic clinical trial.

Methods: 56 healthy adult female (n=26) and male participants (n=30) were randomized to a control arm (Arm A n=6 who had tissue samples taken at two time points one month apart) or to one of 4 intervention arms (n=12 per arm) where a single oral maraviroc 300 mg dose was taken at two time points prior to sampling, one month apart (Arm B: first sampling 2 h post first dose and second sampling 24 h post second dose; Arm C: 4 h and 36 h; Arm D: 6 h and 48 h; Arm E: 12 h and 72 h). Sampling to determine maraviroc concentration included blood, oral fluid and rectal fluid for all. In addition, men provided a urethral swab and a rectal biopsy and women provided a cervico-vaginal aspirate and a vaginal biopsy. Anti-viral activity was assessed by ex vivo challenge with R5-tropic HIV-1_{BaL} of explants cut from mucosal tissue biopsies and measurement of p24 antigen levels in supernatants during 15 days of culture.

Results: Viral replication capacity of HIV-1_{BaL} was significantly reduced (p=0.0005 two-tailed *t*-test) in vaginal biopsies harvested 2h post dosing with p24 levels in culture supernatant at day 15 of culture of 26.74 ± 17.27 pg/ml compared to 200.24 ± 45.89 pg/ml in untreated tissue. No significant reduction of p24 levels were detected at any other time point in vaginal tissue and at no dosing time point in rectal tissue. No Adverse events were reported.

Conclusions: A transient inhibition of ex vivo HIV infection was demonstrated in vaginal tissue 2h after a single oral 300mg maraviroc dose. The lack of inhibition in rectal tissue, despite the ability of Maraviroc to penetrate into the rectum, reveals significant mucosal differences affecting the activity of maraviroc in vaginal and rectal transmission sites. Multi-dosing of maraviroc in humans should be investigated for HIV prevention.

Session O-7 Oral Abstracts — Room 613

10:00 am – 12:15 pm

KS and Cervical/Anal Dysplasia: Tale of 2 Tumors and TB and Other OIs

87 Pomalidomide for Kaposi Sarcoma in People With and Without HIV: A Phase I/II Study

Mark N. Polizzotto[1]; Thomas S. Uldrick[1]; Kathleen M. Wyvill[1]; Karen Aleman[1]; Margaret Bevans[2]; Cody Peer[1]; Douglas Figg[1]; Seth Steinberg[1]; Jerome B. Zeldis[5]; Robert Yarchoan[1]

[1]National Cancer Institute (NCI), Bethesda, MD, US; [2]National Institutes of Health (NIH), Bethesda, MD, US; [3]National Cancer Institute (NCI), Bethesda, MD, US; [4]National Cancer Institute (NCI), Bethesda, MD, US; [5]Celgene Corporation, Summit, NJ, US

Background: Kaposi sarcoma (KS) is a multicentric tumor caused by human herpesvirus 8 and remarkable for its responsiveness to patient immune status. Unmet clinical needs include agents that are oral, anthracycline-sparing, and deliverable in resource limited settings. We evaluated pomalidomide, an oral immunomodulatory agent, in symptomatic KS.

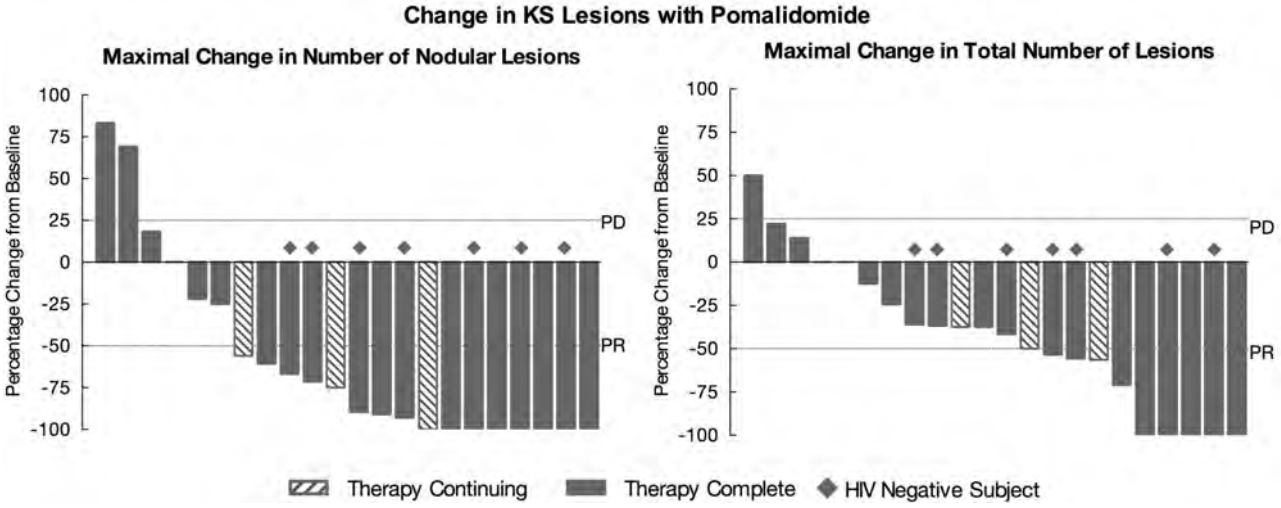
Methods: We performed a prospective phase I/II study to assess the tolerability and pharmacokinetics (PK) of pomalidomide and its anti-tumor activity at the tolerable dose. Primary dose level was 5mg 21 days per 28 day cycle, with a de-escalated level of 3mg if this was not tolerable, and aspirin 81 mg daily as thromboprophylaxis. HIV-infected patients (pts) were eligible if they had controlled viremia and either persistent KS despite 3 months antiretroviral therapy (ART) or progressive KS despite 2 months ART. Evaluations included PK day 1 and 15 cycle 1; KS response by ACTG criteria each cycle; and health related quality of life (HRQL) by FAHI end cycle 3 and end therapy. Study registration NCT1495598.

Results: Primary enrollment completed with 22 pts. All were men; 15 (68%) HIV-infected; med age 50 years (range 32-74); advanced disease (T1) in 16 (72%); prior systemic therapy other than ART in 18 (82%). In HIV-infected, med CD4 429 (135-874); time on ART 48 months (7-227); all HIV VL <50 copies/mL.

No dose limiting toxicities occurred at 5mg and this dose was taken to phase II; all pts were treated at 5mg. Of 148 cycles, grade 3/4 adverse events at least possibly attributable to therapy were: neutropenia (23 cycles [c], 10 pts); CD4 lymphopenia (2 c, 1 pt); and peripheral edema (1 c, 1 pt). Other cytopenias, constipation, rash, and fatigue were common but mild.

15 pts had objective responses (preliminary overall rate 68%, 95% CI 45.1-86.1%): 4 complete (18%) 11 partial (PR, 50%); 4 stable disease (SD, 18%) and 3 progression (13%). 1 pt with SD and 2 with PR continue to improve on therapy. Median time to response 4 weeks (4-36). HRQL showed improved satisfaction with appearance at end therapy (p=0.01), and no impairment during therapy.

PK showed $T_{½}$ 7.1±2.5 hrs, C_{MAX} 61.2±29.3 ng/mL, AUC_{LAST} 624.4±448.4, consistent with prior estimates, no accumulation and no difference by HIV status or ART type.



Waterfall plots show maximal change in the number of nodular lesions (left) and total lesions (right) during therapy for each patient.

Conclusions: Pomalidomide is well tolerated and active in KS regardless of HIV status. Responses were rapid, linked to improved self reported outcomes, and occurred even in advanced and heavily pre-treated KS. Further development could address important unmet needs.

88 Prognostic Model for Patients With Kaposi Sarcoma Treated With ART Alone in Africa

Miriam O. Laker-Oketta[1]; David V. Glidden[2]; Victoria Walusansa[1]; Jackson Orem[1]; A. Rain Mocello[2]; Toby Maurer[2]; Peter W. Hunt[2]; Andrew D. Kambugu[1]; Edward Mbidde[1]; **Jeffrey Martin**[2]

[1]Makerere University College of Health Sciences, Kampala, Uganda; [2]University of California San Francisco, San Francisco, CA, US; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]University of California San Francisco (UCSF), San Francisco, CA, US; [5]University of California San Francisco (UCSF), San Francisco, CA, US

Background: While patients with functionally disabling Kaposi's sarcoma (KS) require chemotherapy for rapid reduction in tumor burden, the management of KS which lacks functionally disabling complications is less certain. This is particularly true in sub-Saharan Africa, where the relative high cost of chemotherapy makes decisions about its use difficult and the use of antiretroviral therapy (ART) alone common as initial KS treatment. However, because a substantial fraction of patients with KS in Africa who are treated with ART alone fare poorly, it would be useful to be able to predict which patients with KS will do well on ART alone versus those who might benefit from additional interventions.

Methods: We studied HIV-infected adults in Uganda with KS with no functionally disabling complications who were initially treated with ART alone as part of the AntiRetrovirals for KS (ARKS) trial. We evaluated the predictive value of 57 variables regarding clinical history, physical exam, laboratory characterization, and radiographic findings, each

measured prior to ART. The outcome was death or KS progression necessitating chemotherapy. The Least Absolute Shrinkage and Selection Operator (LASSO) was used to identify variables with the highest predictive accuracy upon cross-validation.

Results: Among 224 subjects, 44% were women, and median values prior to ART initiation were: 34 years old, 119 CD4+ T cells/mm^3, and 5.3 $\log_{10}$ copies/ml of plasma HIV RNA. The final prediction model had 3 variables: number of anatomic sites with KS, hemoglobin, and Karnofsky performance score. The model showed adequate discrimination: area under the ROC curve = 0.84 (95% CI: 0.78-0.90), and at an optimal cutpoint, the sensitivity for predicting poor outcome was 88% and specificity 74%. Calibration was also good (Figure). At lower probabilities of observed outcome, the model tended to overestimate the probability of poor outcome, while at higher ranges of observed outcome, it slightly underestimated outcomes.

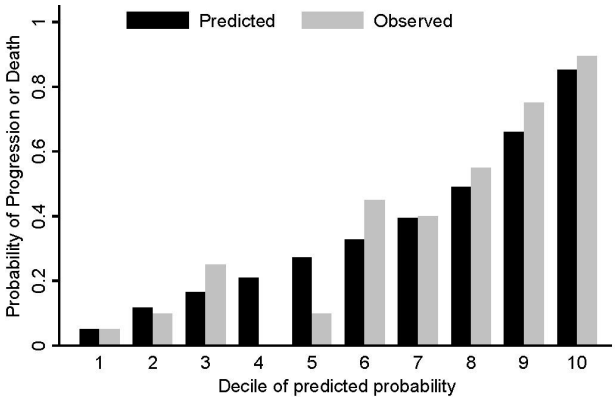


Figure. Calibration of risk prediction model. For each successive decile of predicted probability of progression/death, the mean predicted and observed probabilities for the patients in the decile group are shown.

Conclusions: A prognostic model, consisting of inexpensive measurements, can help to predict which patients in Africa with KS — who present with no functionally disabling complications — will fare poorly when treated with ART alone. The presence of number of KS-containing anatomic sites and hemoglobin in the model suggests the importance of quantitative KS burden in prognosis. The model may help clinicians better advise patients about prognosis and, importantly, inform chemotherapy decisions.

89 One-Year Follow-up of HIV+ Women Screened With VIA, Cytology and HPV in South Africa

Cynthia Firnhaber[1]; Bridgette Goeieman[1]; Lu Mao[2]; Mark Faesen[3]; Simon Levin[3]; Sophie Williams[3]; Avril Swarts[1]; Pam Michelow[1]; Tanvier Omar[1]; Jennifer Smith[2]
[1]University of Witswatersrand, Johannesburg, South Africa; [2]University of North Carolina, Raleigh, NC, US; [3]Right to Care, Johannesburg, South Africa

Background: Cervical cancer is the most common cause of cancer deaths in women in Sub-Saharan Africa. This is due to the burden of the HIV epidemic as well as poor access to screening. Visual inspection with acetic acid (VIA) has been proposed as a screening method for the region, however, there are limited follow-up data for HIV-infected women who have been screened using VIA. This information is needed to inform screening guidelines. We present one year follow up data on a prospective cervical cancer screening study performed in Johannesburg, South Africa.

Methods: HIV-infected women from were rescreened one year later with standard Pap smear and/or colposcopy, VIA and digene HC HPV test, if they had negative or low grade cervical intraepithelial neoplasia (CIN) results at the baseline visit. Associations of progression to higher cervical dyplasia on histology with baseline age, CD4 count, VIA and human papillomavirus (HPV) status were analysed using logistic regression.

Results: A total of 677 of the 1202 women enrolled at baseline were eligible for follow-up and returned at one year. 629 women qualified for colposcopic biopsy and were included in analyses. Median age of the women was 37 years (IQR 32,43). At follow-up, median CD4 count was 387 cells/mm^3 (IQR 250,571) and 93% of the participants were on antiretroviral therapy. Women with CIN 1 and HPV positive results were likely to progress to CIN-2+ [OR 3.63 (1.45-9.1) versus HPV negative]. Women with positive VIA were likely [illegible]e. At one year, 60% (127/211) of the women with either negative [illegible]omen with negative baseline VIA, 18 (4%) progressed to CIN 2+ [illegible]seline were likely to progress at one year [OR 3.09 (1.67-5.72) and

Table. Progression rates, Stratified by Baseline Results.

			Follow-up histology				
Baseline cytology and /or histology	Baseline test results		Negative (N=148)	CIN1 (N=438)	CIN2+ (N=43)	Overall (N=629)	Odds Ratio (CI 95%)
Negative	Overall		84	124	3	211	
	VIA	Negative	83	106	3	192	REF
		Positive	1	18	0	19	13.35 (1.73-102.8)
	HPV	Negative	62	89	1	152	REF
		Positive	22	35	2	59	1.0 (0.52-1.92)
CIN1	Overall		64	314	40	418	
	VIA	Negative	44	186	15	245	REF
		Positive	20	128	25	173	1.85 (0.92-3.72)
	HPV	Negative	32	142	6	180	REF
		Positive	31	172	34	237	3.63 (1.45-9.1)

CIN: cervical intraepithelial neoplasia; HPV: human papillomavirus; VIA: Visual inspection with acetic acid

Conclusions: At one year follow-up, HIV-infected women who were VIA positive at baseline were more likely to progress from negative to CIN 1+ and from CIN 1 to CIN 2+. Of women with negative baseline VIA, 4% progressed to CIN 2+ in a year. HIV-infected women with a positive VIA or HPV should be screened at one year for possible progression.

90 High Rate of HSIL on HRA in HIV+ Women Not Meeting Criteria for Anal Cancer Screening

Michael M. Gaisa; **Fanny Ita-Nagy**; Gabriela Rodriguez Caprio; Michael Mullen; Judith Aberg; Michelle Cespedes
Icahn School of Medicine at Mount Sinai, New York, NY, US

Background: HIV-infected patients have a higher burden of HPV associated high-grade squamous intraepithelial lesions (HSIL) and anal cancer. Guidelines for anal cancer screening in HIV-infected women in New York State include a history of abnormal cervical and/or vulvar histology or history of anogenital warts. The HIV Medical Association of IDSA (HIVMA) screening guidelines include these and add "or a history of receptive anal intercourse" to the criteria as another indication. Best practices for this population are poorly defined. Here we report outcomes and associated risk factors for HSIL in HIV-infected women over five years after implementation of a program which offers anal cancer screening by means of anal cytology to all HIV-infected women regardless of previous HPV disease or sexual behavior.

Methods: Data from women who underwent high resolution anoscopy (HRA) following abnormal anal cytology from April 2009 to July 2014 were reviewed. All HRA were performed by a single operator. Routine clinical data included cervical PAP history, demographics, behavioral data, and HRA results. Chi square tests were used for comparisons.

Results: 306 HIV-infected women underwent HRA, median age was 47, mean CD4 was 537 cells/mm^3, 67% had HIV viral loads <50, 72% had a history of abnormal cervical PAP, and 66% reported a history of anal receptive intercourse. HSIL was found in 28% of anal biopsies. 49% of the 55 women who did not meet criteria for anal cancer screening according to NYS guidelines had anal dysplasia on biopsy. 13 of the 55 women (24%) had HSIL requiring treatment, including one subject with minimally invasive carcinoma. Using HIVMA recommendations, an additional 35 patients met criteria for anal cancer screening. Four of the 20 women (20%) who did not meet screening criteria by either guideline had HSIL on biopsy. Neither meeting NYS criteria, HIVMA criteria, nor a history of receptive anal intercourse as the sole criterion were significantly associated with a diagnosis of HSIL (p=0.079, 0.403, and 0.093 respectively). A history of smoking was the only factor associated with HSIL on biopsy (p=0.002).

Prevalence of HSIL on HRA in HIV Infected Women by Screening Guideline Recommendations

	meets guideline criteria for screening	Number meeting criteria per category	Abnormal lesion on anal biopsy	LSIL on anal biopsy	HSIL on anal biopsy
NYS DOH AIDS Institute Guidelines	Y	251	165	104	61
	N	55	19	10	9
HIVMA of IDSA Primary Care Guidelines	Y	286	184	114	70
	N	20	8	4	4

Conclusions: Anal HSIL was commonly found in HIV-infected women in this cohort. A high rate of dysplasia on biopsy was found even among women who did not meet criteria for routine screening. These results support that all HIV infected women may benefit from anal cancer screening regardless of their cervical / genital HPV history or sex practices.

91 Xpert MTB/RIF Ultra: A New Near-Patient TB Test With Sensitivity Equal to Culture

David Alland[1]; Mazhgan Rowneki[1]; Laura Smith[1]; Jamie Ryan[2]; Mitchell Chancellor[2]; Ann Marie Simmons[2]; David Persing[2]; Robert Kwiatkowski[2]; Martin Jones[2]; Soumitesh Chakravorty[1]
[1]*Rutgers New Jersey Medical School, Newark, NJ, US;* [2]*Cepheid, Sunnyvale, CA, US*

Background: The Xpert MTB/RIF (Xpert) assay, the first near-patient test for tuberculosis (TB), detects *Mycobacterium tuberculosis* (*Mtb*) with a limit of detection (LOD) of 133 CFU/ml sputum, and detects mutations in the *Mtb rpoB* gene which cause Rifampicin resistance (RIF-R). However, despite high sensitivity overall, Xpert sensitivity is only 60 – 80% in smear-negative TB. Also, small numbers of false RIF-R have been reported recently, usually due to abnormal real-time PCR curves or miss-identification of RIF-susceptible (RIF-S) synonymous *rpoB* mutants as RIF-R. A new molecular TB test with an LOD equivalent to the 10 – 100 CFU/ml LOD of liquid culture and improved RIF-R detection is needed.

Methods: For the Xpert MTB/RIF Ultra (Ultra) assay, we developed a new sample processing cartridge that doubled the amount of purified DNA delivered to the PCR reaction. Four newly designed probes that detected mutations in *rpoB* gene replaced the five Xpert real-time probes. Real-time *Mtb* detecting probes targeting IS6110 and IS1081 were added. Cartridge fluidics and PCR cycling were optimized. Assay LODs were tested by spiking *Mtb* H37Rv and BCG cells into sputum samples, treating with Sample Reagent, splitting samples, and testing with Xpert and Ultra. RIF-R detection was tested with a panel of 30 different RIF-R *Mtb rpoB* mutants. LOD was defined as the lowest CFU that could be detected in at least 19/20 (95%) tests.

Results: Ultra was significantly more sensitive than Xpert. In sputum samples spiked with *Mtb* H37Rv, Ultra had an LOD of 5 CFU/ml compared to an LOD of 50 CFU/ml for Xpert (p=0.001). In sputum samples spiked with BCG, Ultra had an LOD of 25 CFU/ml compared to an LOD of 165 CFU/ml for Xpert (p=0.01). Ultra detected 30 different RIF-R *Mtb rpoB* mutants as RIF-R (sensitivity 100%). None of the 25 RIF-S *rpoB* wild type samples and none of the 3 RIF-S synonymous *rpoB* Q513Q (1) and F514F (2) mutant samples were detected as RIF-R (specificity 100%). Ease of use was identical for Xpert and Ultra.

Conclusions: The new Ultra assay is much more sensitive than Xpert, and is likely to be as sensitive as liquid TB culture. Ultra detects RIF-R as efficiently as Xpert; but the specificity of Ultra RIF-R is likely to be higher due to improvements in assay design. The Ultra assay should significantly increase TB detection in smear-negative patients and provide more reliable RIF-R detection.

92 Majority of XDR TB Cases Are Due to Transmission in a High-HIV-Prevalence Setting

N. Sarita Shah[1]; James C. Brust[2]; Barun Mathema[3]; Thuli Mthiyane[4]; Nazir Ismail[5]; Pravi Moodley[6]; Koleka Mlisana[8]; Salim Allana[7]; Jonathan Smith[7]; Neel R. Gandhi[7]

[1]US Centers for Disease Control and Prevention, Atlanta, GA, US; [2]Montefiore Medical Center & Albert Einstein College of Medicine, Bronx, NY, US; [3]Columbia University Mailman School of Public Health, New York, NY, US; [4]University of KwaZulu-Natal, Durban, South Africa; [5]National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg, South Africa; [6]University of KwaZulu-Natal & National Health Laboratory System, Durban, South Africa; [7]Emory University Rollins School of Public Health, Atlanta, GA, US; [8]University of KwaZulu-Natal & National Health Laboratory Service, Durban, South Africa

Background: Drug-resistant TB threatens gains made in the control of TB and HIV worldwide. In South Africa, there has been a ten-fold increase in the number of MDR and XDR TB cases over the past decade. Factors driving this rapid rise in caseload have not been fully elucidated. We sought to determine the proportion of XDR TB cases resulting from primary transmission versus inadequate treatment of MDR TB (i.e., acquired resistance).

Methods: Cross-sectional study of 400 culture-confirmed patients with XDR TB diagnosed during 2011–2014 from KwaZulu-Natal province, South Africa. Participants were interviewed about demographics, previous TB and HIV history, healthcare utilization, and potential TB exposures. Medical records were reviewed for prior treatment with first- and second-line TB medications and previous hospitalizations. All *M.tuberculosis* isolates underwent IS*6110* RFLP genotyping and targeted sequencing of nine resistance-conferring genes. Isolates from genotypic clusters with more than 20 participants also underwent whole genome sequencing.

Results: To date, 377 patients with XDR TB have been enrolled. The median age was 33 (IQR 29-43) and 57% were female. 78% were HIV-infected, with a median CD4 count of 275 cells/mm^3 (IQR 149 – 433); 90% were on antiretroviral therapy at the time of enrollment and 79% had a viral load <400 copies/ml. Participants were identified from all 11 districts in the province. Only 33% of participants had been previously treated for MDR TB, and an additional 7% had received fluoroquinolones or injectable TB medications for non-TB illnesses. Based on genotypic analysis, 87% of participants had an isolate that belonged to one of 16 clusters; only 13% had isolates that were unique. One large cluster (LAM4/KZN) accounted for 47% of participants, while the remaining cluster sizes ranged from 2–16 participants. Whole genome sequencing confirmed the highly clonal nature of the large LAM4/KZN cluster.

Conclusions: In this high HIV prevalence setting, the majority of XDR TB cases occurred due to transmission of drug-resistant TB strains, rather than prior inadequate treatment of MDR TB. Analysis of epidemiologic and geospatial data also collected in this study will provide valuable insights into identifying potential locations of transmission and opportunities to intervene. TB control efforts must focus on curbing transmission through improved TB case-finding, infection control and enhanced treatment programs.

93 Linkage to HIV/TB Care in South Africa: A Randomized Trial of Health Navigators

Ingrid V. Bassett[2]; Sharon M. Coleman[1]; Janet Giddy[4]; Laura M. Bogart[3]; Christine E. Chaisson[1]; Douglas Ross[5]; Tessa Govender[4]; Kenneth A. Freedberg[2]; Rochelle P. Walensky[2]; Elena Losina[2]

[1]Boston University School of Public Health, Boston, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Boston Children's Hospital, Harvard Medical School, Boston, MA, US; [4]McCord Hospital, Durban, South Africa; [5]St. Mary's Hospital, Mariannhill, South Africa

Background: Despite increases in HIV testing, only a fraction of those newly diagnosed with HIV enter care and initiate ART promptly in South Africa. Our objective was to establish the efficacy of health system navigators for improving linkage to HIV care and TB treatment completion among newly diagnosed HIV-infected outpatients in Durban, South Africa.

Methods: We conducted a randomized controlled trial (Sizanani Trial, NCT01188941) among adult (≥18y) patients enrolled at 4 sites (2 hospital outpatient departments and 2 primary health clinics) prior to HIV diagnosis. HIV-infected participants underwent TB screening with sputum microscopy and culture and were randomized to receive a health system navigator intervention or usual care. Participants in the usual care arm received care according to each clinic's practice. Participants in the navigator arm had a baseline interview using a strengths-based case management approach to assist in identifying barriers to entering care and devising solutions, and then received scheduled phone calls and text messages over 4 months. The primary outcome was 3 months on ART and alive for those ART-eligible at baseline or completion of 6 months of TB treatment. We assessed outcomes via medical records at study sites and the South African death registry 9 months after enrollment.

Results: Of 6,536 subjects screened, 4,903 were eligible and enrolled; 49% were female and mean age was 34 years (SD 13). 1,899 (39%) subjects were HIV-infected, of whom 1,146 (60%) were ART eligible; 369 (19%) were co-infected with TB. In the usual care arm, 197 (21% of HIV-infected and 37% of ART eligible) reached the primary composite study outcome, compared to 212 (22% and 34%, respectively) in the navigator arm (p=0.60). 250/1,899 (13%) HIV-infected subjects died during the study period; there was no difference in death rates between study arms.

Conclusions: Less than 40% of ART-eligible individuals newly diagnosed with HIV in Durban had evidence of taking ART for ≥3 mo or completing TB treatment at the study sites during the nine months after diagnosis. This RCT did not provide evidence that a health navigator-based intervention improves ART initiation or TB treatment completion. Low rates of engagement and retention in care, coupled with the lack of efficacy of the navigator intervention, highlight the urgency of identifying more effective strategies for improving HIV and TB care outcomes.

94 Is It Safe to Stop Cotrimoxazole in Adults on ART: COSTOP, a Noninferiority RCT

Paula Munderi[1]; **Jonathan B. Levin**[1]; Zacchaeus Anywaine[1]; Ronnie Kasirye[1]; Anatoli Kamali[1]; Andrew J. Nunn[2]; Heiner Grosskurth[3]
On behalf of COSTOP Research Team

[1]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda; [2]University College London, London, United Kingdom; [3]London School of Hygiene and Tropical Medicine, London, United Kingdom

Background: In Uganda, cotrimoxazole (CTX) prophylaxis is recommended as part of a package of comprehensive care. The benefits of continuing CTX in African patients who have regained immune competence through ART are not known particularly in the light of potential disadvantages such as co-toxicity with ART and increased pill burden leading to possible diminished adherence to HIV treatment The objective of COSTOP was to assess the risks and benefits of discontinuing CTX in patients achieving sustained immune restoration.

Methods: From January 2011 HIV-infected patients aged ≥18 years, stable on ART with confirmed CD4 restoration to 250 cells/mm3 and above who consented to join the double-blind trial were randomised 1:1 to one oral tablet of 960 mg of CTX daily or matching placebo. Co-primary outcome measures were (1) time to first CTX-preventable event excluding malaria, (2) time to the occurrence of the first grade 3 or 4 haematological adverse event (AE). Patients attended study clinics monthly during the first 3 months post-randomisation and 3-monthly thereafter for a range of 1 – 3 years. An endpoint review committee adjudicated the efficacy endpoints.

The analysis of the efficacy assesses the non-inferiority of the outcome in the placebo arm compared to the control; non-inferiority required the upper limit of the 90% confidence interval to be less than a 25% increased risk of an endpoint event on the placebo arm. The primary safety analysis assesses the reduction in haematological adverse events in the placebo arm. The study had a minimum of 80% power based on assumptions concerning endpoints in the CTX arm.

Results: 2180 patients were enrolled from two sites in SW Uganda; 74% female, median age 41, CD4 count 518, months on ART 48. 93.3% patients completed at least a year in the study. In the per protocol analysis a total of 124 (54 CTX, 70 placebo) first CTX preventable adjudicated events occurred, hazard ratio adjusted for site and CD4 stratum (aHR) 1.35

(90% CI 1.00,1.81), a difference of 0.9/100 person years. These findings were confirmed in ITT and sensitivity analyses. The incidence of first grade 3 or 4 haematological adverse events was reduced in the placebo arm, aHR 0.70, 95% CI 0.59, 0.82.

Conclusions: Although there was a significant reduction in grade 3 or 4 haematological adverse events in patients allocated to stopping CTX non-inferiority of this strategy with respect to CTX preventable events was not demonstrated.

95LB High-Dose Rifampin, SQ109 and Moxifloxacin for Treating TB: The PanACEA MAMS-TB Trial

Martin J. Boeree[1]; Michael Hoelscher[2]
On behalf of the PanACEA consortium
[1]*Radboudumc, Nijmegen, Netherlands;* [2]*University of Munich, Munich, Germany*

Background: Shorter regimens are urgently needed for the treatment of TB. The PanACEA MAMS-TB trial was conducted to evaluate whether 12-week combinations of high-dose rifampin, SQ109 and moxifloxacin with standard drugs reduced time to culture conversion on liquid media sufficiently to select for a phase III treatment-shortening trial.

Methods: Adult patients with drug-sensitive smear-positive TB were randomly allocated in the ratio 1:1:1:1:2 to be treated for 12 weeks of 1) Q: SQ109 together with standard dose rifampin (R), isoniazid (H) and pyrazinamide (Z), 2) 20RQ: SQ109 and 20 mg/kg R together with ZH, 3) 20RM: moxifloxacin and 20mg/kg R together with ZH, 4) 35R: 35mg/kg R together with ethambutol (E) and HZ, and a control arm for 8 weeks with standard RHZE. All patients then received standard RH to complete a total of 26 weeks of treatment, and were followed for treatment failure and relapse. The trial had a multi-arm multi-stage (MAMS) design with one interim analysis where recruitment to arms could be stopped due to lack of benefit based on pre-specified stopping rules.

Results: 365 patients were randomised from 7 sites in Tanzania and South Africa, of whom 25 (7%) were HIV positive. Recruitment to both SQ109 arms was terminated after the interim analysis; patients on these arms remained on treatment and in follow-up. At the final analysis, covariate-adjusted hazard ratios compared to control over 12 weeks were 0.82 (Q, 95% CI 0.55-1.24), 0.73 (20RQ, 0.48-1.13), 1.42 (20RM, 0.98-2.05), and 1.75 (35R, 1.21-2.55). For comparison to previous TB trials, covariate-adjusted hazard ratios compared to control over 8 weeks were 1.69 (1.02-2.80) for 20RM and 1.99 (1.21-3.29) for 35R. This is the largest reduction in time to culture conversion seen in any previous TB trial to our knowledge. Grade 3 or higher adverse events were experienced by 7(12%) Q, 7(12%) 20RQ, 9 (14%) 20RM, 9(14%) 35R and 12(10%) control patients, of which 1, 5, 7, 4 and 5 were considered at least possibly related to treatment. Hepatic adverse events leading to a change in treatment were experienced by 10 (2.7%) patients.

Conclusions: These data suggest that 35mg/kg rifampin may reduce the time to culture conversion and may be an important component in future treatment-shortening regimens. For 20mg/kg rifampin and moxifloxacin there was a modest reduction; there was no reduction with SQ109. Adaptive designs such as MAMS are feasible for multi-centre TB clinical trials and could speed regimen development.

Session O-8 Oral Abstracts — Room 6E

10:00 am – 12:.30 pm

Factors Affecting HIV Care and Outcome: Global Perspective

96 Special Presentation: PEPFAR 3.0: Controlling the Epidemic and Delivering on the Promise of an AIDS-Free Generation

Ambassador Deborah L. Birx
US Department of State, Washington, DC, US

97 Joint Estimation of HIV Progression and Survival: A Pooled Analysis of 25 Countries

Tara D. Mangal
On behalf of the UNAIDS Working Group on CD4 Progression and Mortality Among HIV Seroconverters including the CASCADE Collaboration in EuroCoord
Imperial College London, London, United Kingdom

Background: National estimates of antiretroviral treatment (ART) need and coverage, based on CD4 cell count thresholds, are generated by most countries using the Spectrum model. This uses model parameters for survival and CD4 progression that are derived from separate analyses. We developed a model which simultaneously estimates CD4 decline and survival in HIV-positive individuals by age, sex, and geographic region. We use the largest pooled dataset to date, collating data from 50 HIV seroconverter cohorts and collaborations in Africa, Europe, North America and Asia.

Methods: We used a hidden Markov model to describe survival and CD4 decline following seroconversion in the absence of ART. The model estimates forward-only transition rates through six transient states characterised by ranges of decreasing CD4 levels, towards two absorbing states, corresponding to ART initiation and death. We stabilised variability in CD4 counts using a log transformation. Natural short-term fluctuations along with measurement errors in CD4 cell counts were accounted for using a normal measurement error model. Covariates were included on the transition rates and survival probabilities were estimated for each subgroup.

Results: The 27,511 eligible individuals had a median follow-up time of 3.55 (IQR 1.71, 6.20) years, were predominantly male (74.1%) and had a median age at seroconversion of 29.1 (IQR 24.4, 35.4) years. Of these individuals, 23,031 had recorded CD4 counts pre-ART, 1943 died, and 14,519 initiated ART. Median (95% CI) survival for males aged 20 years at seroconversion was 11.6 (10.6-12.1), 11.3 (10.5-11.7) and 9.0 (8.7-9.4) years in Africa, Europe/North America and Asia, respectively. The mean time from seroconversion to CD4 counts <500 cells/mm^3 for males in Africa aged 20 years was 3.02 years, conditional on starting above 500 cells/mm^3. Transition rates and all-cause mortality rates progressively increase with increasing age (hazard ratio [HR] 1.02, 95% CI 1.02-1.03 for every five years of age for CD4 stages, HR 1.17, 95% CI 1.17-1.18 for mortality).

Conclusions: CD4 decline and mortality after HIV infection in the absence of ART was similar in African, European and North American cohorts, but significantly faster for all ages in Asian cohorts. Older age is associated with an increased hazard for progression. Joint estimation of these parameters reveals heterogeneities between regions and ages, which should be incorporated into future HIV models to accurately estimate ART need and coverage.

98 Impact of Emergency Department HIV Testing and Linkage to Care: 25 Years' Experience

Gabor Kelen[3]; Eshan U. Patel[2]; Yu-Hsiang Hsieh[3]; Oliver B. Laeyendecker[2]; Judy Shahan[3]; William Clarke[3]; Jordyn L. Manucci[3]; Richard Rothman[3]; **Thomas C. Quinn**[2]
[1]*Johns Hopkins University School of Medicine, Baltimore, MD, US;* [2]*National Institute of Allergy and Infectious Diseases (NIAID), Baltimore, MD, US;* [3]*Johns Hopkins University School of Medicine, Baltimore, MD, US*

Background: The Johns Hopkins Hospital (JHH) Emergency Department (ED) has served as both an observational window on the HIV-epidemic for over 25 years, and as a pioneer in ED-based testing and linkage to care programs. We document the changing nature of the local epidemic in inner city Baltimore and the success of ED-based strategic approaches to curtail the epidemic.

Methods: We analyzed 7 discrete identity-unlinked serosurveys conducted on 18,240 untargeted adult JHH-ED patients between 1987-2013 for demographic trends in HIV prevalence, cross-sectional incidence estimates, viral load and HCV prevalence. JHH ED HIV testing and linkage to care programs were initiated in 2005 and continue to date.

Results: HIV prevalence in 1987 was 5.2%, peaked at >11% from 1992-2003, and then declined to 5.6% in 2013. While seroprevalence was highest for black males, (initial 10%, peak 20%, last 10%), and lowest for white females, the time trend for prevalence was consistent for all groups. Proportion of undiagnosed HIV declined over time from 77% in 1987, 28% in 1992, and 12% by 2013 ($p<0.001$). HIV incidence estimates in 2001 were 2.1% and declined steadily to 0.16% by 2013 ($p<0.001$). Proportion of HIV+ individuals with viral suppression (<400 c/ml) increased steadily from 23% in 2001 to 59% by 2013 ($p<0.001$). Consistent with increasing viral suppression, 80% of 214 HIV+ individuals surveyed in 2013 had antiretroviral drugs detected in their sera, a marked increase from 2007 (27%) ($p<0.001$). The trends in improved outlook were consistent in all demographic subgroups. However, HCV in this population remained at 18-19% from 1988 until 2007 and declined only slightly to 14% by 2013. Dual HIV/HCV infection remained relatively stable (48%-52%) from 2007 to 2013.

Conclusions: Over a 25-year period, JHH ED-based HIV testing evolved from describing the local epidemic to playing a major strategic role in locally controlling the epidemic. This is evidenced by declining undiagnosed HIV infection, increased use of ARVs with increasing viral suppression and a consequential decline in incidence among JHH ED patients. While causation is not directly addressed, the improvements in HIV status in this population coincide with JHH ED-based testing, while the linkage to care program is associated with increased ARV therapy. Noting only a comparative slight decrease in HCV infection in the same population underscores the potential for a causal relationship.

99 Linkage to Care and Viral Suppression Among New HIV Diagnoses, New York City, 2006-13

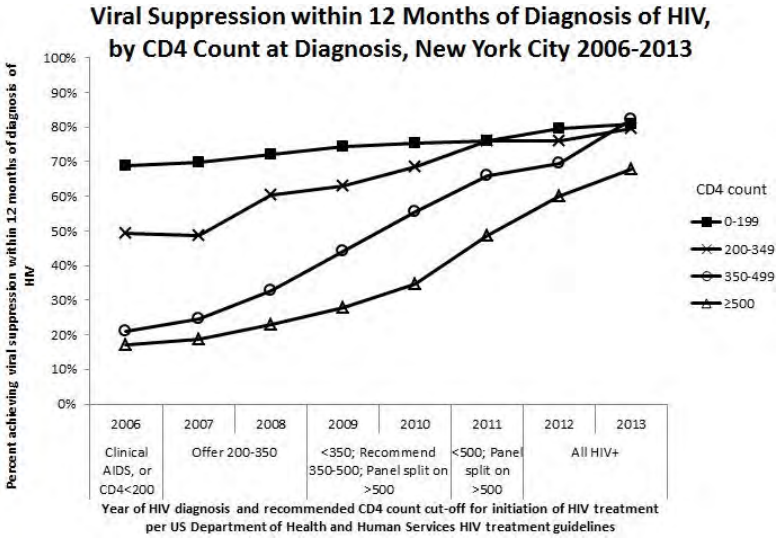
Ellen W. Wiewel; **Lucia V. Torian**; Qiang Xia; Sarah L. Braunstein

New York City Department of Health and Mental Hygiene, Long Island City, NY, US

Background: Since 2007, US Department of Health and Human Services (DHHS) HIV guidelines have advocated timely linkage to medical care (LTC) and progressively earlier initiation of antiretroviral therapy (ART) after diagnosis. A 2010 New York State law required LTC for consenting newly diagnosed persons. Less-immunocompromised and younger adults have historically had lower rates of LTC and viral suppression (VS). Trends in LTC and VS in New York City (NYC) can indicate provider uptake of new guidelines and whether differences in outcomes by immune status and age have been reduced.

Methods: Using NYC HIV surveillance registry data as of 6/30/2014, we calculated timely LTC and VS among residents 18+ years newly diagnosed in 2006-13 who survived >91 days post-diagnosis, overall and by CD4 count and age at diagnosis. Timely LTC was defined as CD4 or viral load (VL) test 8-91 days post-diagnosis. VS was defined as VL ≤400 copies/mL, measured by 6, 9, and 12 months post-diagnosis. CD4 count at diagnosis was imputed from value and timing of first CD4, assuming 50-cell/year decrement, and categorized in intervals of 0-199, 200-349, 350-499, and ≥500 cells. Trends by diagnosis year were assessed by Cochran-Armitage and differences by CD4 and age by Chi-square.

Results: Timely LTC increased overall (68% to 76%, $p<0.0001$) and across all CD4 intervals and all age groups <55; LTC did not change for persons ≥55. VS also increased overall (24% to 54% by 6 months, 32% to 65% by 9, and 36% to 69% by 12, all $p<0.0001$) and for all CD4 intervals and age groups. Percent VS by 12 months nearly quadrupled for persons with CD4 ≥350 (19% to 73%) and more than doubled for persons 18-34 (30% to 66%). Concordant with changes in guidelines, increases in LTC were steepest in 2010-11, and increases in VS escalated in 2007-8 for persons with CD4 200-349, 2008-11 for 350-499, and 2010-12 for CD4 ≥500 (Figure). In 2006, LTC and VS at 12 months differed across CD4 intervals and age groups ($p<0.0001$). However, by 2013, differences were observed only between persons with CD4 <500 and ≥500.



Conclusions: Timely LTC and VS increased over the entire period (2006-13) among persons newly diagnosed and reported with HIV in NYC, overall and in most CD4 and age groups. Some larger year-over-year increases in LTC and in VS by CD4 follow updated recommendations. These favorable trends notwithstanding, as of 2013, NYC was still far from the ideal of timely LTC and VS for all newly diagnosed residents.

100 Care and Viral Suppression Among Women, 18 US Jurisdictions

Ndidi Ike; Angela L. Hernandez; Qian An; Taoying Huang; H. Irene Hall

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: Women comprise 25% of persons living with HIV in the United States. The HIV diagnosis rate for black and Hispanic women is 19 and 3.5 times, respectively, the rate for white women. Overall, disparities also exist in care and treatment outcomes by race/ethnicity. We assessed differences in care and viral suppression among women.

Methods: We used data from the National HIV Surveillance System reported from 18 US jurisdictions to determine care and viral suppression among women aged ≥13 years. Linkage to care, defined as ≥1 CD4 or viral load (VL) test within 3 months of diagnosis, was assessed for women diagnosed in 2012. Retention in care (i.e., ≥2 CD4 or VL tests at least 3 months apart in 2011) and viral suppression (i.e., most recent VL ≤200 copies/mL in 2011) were determined for women living with HIV during 2011. Data were statistically adjusted for missing HIV transmission categories.

Results: Among 3,903 women diagnosed with HIV in 2012, 83% were linked to care. Women aged 13-24 years had the lowest percentage of linkage to care compared to those aged ≥55 years (78% vs. 85%). Similar percent distributions by age were observed in all race/ethnicity groups. Among 102,726 women living with HIV in 2011, 52% were retained in care. The percentage in care was higher among older women (≥ 55 years, 57%) compared with younger women (e.g., 13-24, 54%; 25-34, 46%). The percentage retained in care was comparable among blacks (48%) and whites (51%) but higher among Hispanics (59%); the percentage was lowest among American Indians/Alaska Natives (33%). Overall,

44% of women had a suppressed viral load and it was higher among older (≥ 55 years, 53%) compared with younger women (13-24 years, 33%). Viral suppression was highest among Hispanics (49%), followed by Asians (48%), whites (47%), and blacks (42%), and lowest among American Indians/Alaska Native (30%). Retention in care was similar but viral suppression was lower among women who inject drugs (42%) compared with heterosexual women (46%).

Conclusions: Almost half of women living with HIV were not in regular HIV care, and retention in care and viral suppression differed by race/ethnicity and age. Black-white differences in viral suppression among women are smaller than previously observed for men and women combined. Improvements in care and treatment outcomes are needed for all women, with particular focus on younger women.

101 Time Above 1500 Copies/ml: A Viral-Load Measure for Assessing Transmission Risk of HIV-Positive Patients in Care

Lytt I. Gardner[1]; Gary Marks[1]; Charles Rose[1]; Meg Sullivan[2]; Susan Holman[3]; Jeanne Keruly[4]; Anne Zinski[5]; Allan Rodriguez[6]; Thomas Giordano[7]

[1]Centers for Disease Control and Prevention, Atlanta, GA, US; [2]Boston University School of Medicine, Boston, MA, US; [3]Colleges of Medicine and Nursing, SUNY Downstate Medical Center, Brooklyn, NY, US; [4]Johns Hopkins University School of Medicine, Baltimore, MD, US; [5]University of Alabama at Birmingham, Birmingham, AL, US; [6]Miller School of Medicine, University of Miami, Miami, FL, US; [7]Baylor College of Medicine, Houston, TX, US

Background: HIV-positive persons aware of their serostatus account for about 50% of HIV transmissions. As entry and retention in care improves, proportionally more of these transmissions will come from HIV patients in care. We assessed the HIV transmission potential of patients in care by examining the amount of person-time (PT) they spend above a viral load (VL) threshold that increases risk for transmission.

Methods: The analysis included 14,532 HIV patients in six HIV clinics in the U.S. from April 1, 2009 to March 31, 2013. We examined HIV transmission potential by using longitudinal cohort data on VLs and amount of PT spent above a VL threshold (1500 copies/ml) that increases risk for transmission. Eligible patients had to have ≥30 days between their first and last VL test (total observation time). Consecutive VLs and the duration between them were used to generate PT: when two consecutive results were ≤1500 copies, then all PT was below the threshold; when two consecutive results were >1500 copies, then all PT was above the threshold; when one result was above and the other one below the threshold, then PT was estimated based on the magnitude of the difference in the two VLs and the extent to which the larger VL exceeded the 1500 copies/ml threshold. Poisson regression with robust standard errors was used to estimate the rate (percent) of PT above the threshold. A multivariable model of time above the 1500 copies threshold controlled for demographic and clinical predictors.

Results: Overall, the HIV VL exceeded 1500 copies/ml during 23% of patients' observation time (average, 84 days per person, per year); 54% of the patients had one or more VLs above 1500. In the multivariable model, the percentage of PT above the 1500 threshold was significantly higher among: patients aged 16 to 39 (32%) and 40 to 49 (23%) vs. 50+ years (16%) ; black (26%) vs. white (16%) patients; those who injected drugs (26%) vs. those who did not (23%); patients with an initial VL >1500 copies/ml (51%) vs. <1500

Estimate of percentage of person-time with viral load (VL) exceeding 1500 copies/ml, by demographic and clinical subgroups, Retention in Care Study, 2009-2013.

Subgroups	Subgroup N (%)	% of observation time VL exceeded 1500 copies/ml	95% CI	Unadjusted rate ratio	95% CI	Multivariable adjusted rate ratio	95% CI
Overall	14,532	23.08	22.51, 23.66				
Age at time of initial VL in analysis							
16-39	4415 (30.4)	32.12	30.93, 33.36	1.95	1.83, 2.08	1.51	1.42, 1.59
40-49	5228 (36.0)	22.77	21.85, 23.74	1.38	1.30, 1.48	1.26	1.19, 1.33
50-85	4889 (33.6)	16.47	15.66, 17.32	ref.		ref.	
Race/ethnicity							
Black	9246 (63.6)	26.08	25.34, 26.85	1.63	1.50, 1.76	1.23	1.14, 1.32
Hispanic	2640 (18.2)	19.65	18.44, 20.93	1.22	1.11, 1.35	0.92	0.84, 1.00
Other	220 (1.5)	12.39	9.27, 16.57	0.77	0.57, 1.04	0.67	0.51, 0.86
White	2426 (16.7)	16.04	14.88, 17.31	ref.		ref.	
Gender/orientation							
MSM	4460 (30.7)	20.09	19.14, 21.08	0.85	0.80, 0.91	0.92	0.87, 0.98
Women	4983 (34.3)	25.09	24.10, 26.13	1.06	1.00, 1.13	1.01	0.96, 1.06
Heterosexual Men	5089 (35.0)	23.64	26.70, 24.65	ref.		ref.	
Injection drug use as risk factor for HIV acquisition							
Yes	1933 (13.3)	25.63	24.04, 27.33	1.13	1.05, 1.21	1.30	1.20, 1.36
No	12599 (86.7)	22.69	22.08, 23.31	ref.		ref.	
Viral load > 1500 copies/ml as initial VL in analysis							
Yes	5479 (37.7)	50.81	49.72, 51.93	4.85	4.60, 5.11	4.21	3.96, 4.46
No	9053 (62.3)	10.48	10.00, 10.98	ref.		ref.	

Conclusions: Several subgroups of HIV-positive patients in care spent a quarter or more of their time with VLs above 1500 copies/ml, putting them above the threshold for potentially transmitting HIV to others. Efforts by HIV clinicians and patients to maximize the duration of time with VL below 1500 copies/ml will reduce the risk of HIV transmission.

102 Incidence and Risk Factors for Sexual Assault Among MSM and Young Women in Coastal Kenya

Adrian D. Smith[1]; Sam Rogers[1]; Elizabeth Wahome[2]; Marianne Darwinkel[2]; Susan M. Graham[3]; Eduard J. Sanders[2]

[1]Nuffield Department of Population Health, Oxford, United Kingdom; [2]Centre for Geographic Medicine Research – Coast, Kilifi, Kenya; [3]University of Washington, Seattle, WA, US

Background: Experience of rape presents direct and indirect risks for HIV transmission. Sex workers and men who have sex with men (MSM) in Africa are widely criminalized and may experience discrimination in interactions with public and organised society.

Methods: Data were from cohorts of HIV-negative and HIV-positive adults in Coastal Kenya since 2005. Follow-up included periodic risk behaviour assessment, including occurance of rape in the prior 3 months. Incidence of first rape was estimated for male and female participants separately. We estimated adjusted odds ratios (AOR) of rape for

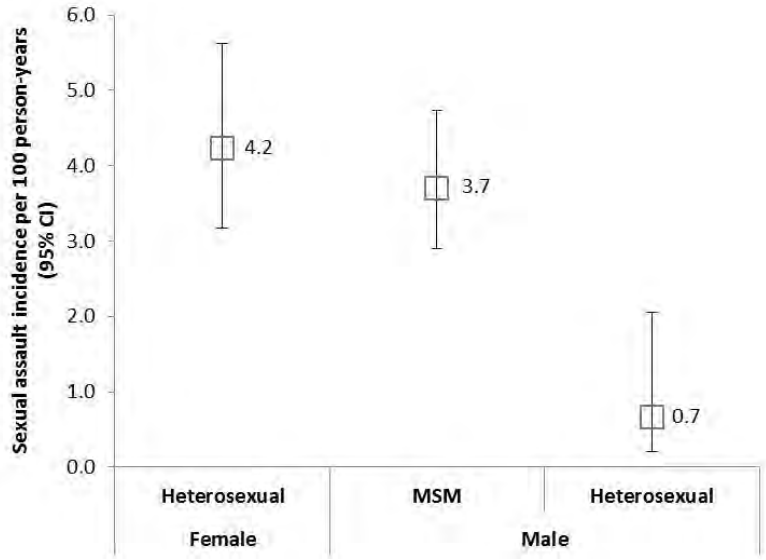
sociodemographic and behavioral covariates reported at each follow up visit using generalized estimating equations with a logit link and HIV incidence rate ratios (IRR) using Poisson regression for MSM who were HIV negative at enrolment.

Results: 1,425 adults were enrolled: 970 men (727 MSM and 243 heterosexual men) and 455 women. 86.1% of MSM, 29.2% of heterosexual men and 80.7% females reported selling sex during follow up.

8.8% MSM, 1.2% heterosexual men and 10.3% women reported being raped at least once during follow-up (rates in figure). Assailants were often family members or neighbours (MSM: 49.5% (64/727); females 55.7% (47/455) whilst 10% were public officials (MSM: 9.5%; females: 9.8%). MSM assailants were more likely to be strangers (26.7% MSM assaults vs. 9.8% female assaults p=0.010).

For men, rape was associated with selling sex in the past 3 months (AOR 3.8 [1.7-7.4] p<0.001), behavioural orientation (exclusive MSM: AOR 4.4 [1.0-18.1], bisexual MSM: 1.7 [0.4-6.9] vs. heterosexual orientation, p=0.012); young age (18-24 yrs: AOR 12.5 [1.1-138.0], 25-34 yrs: AOR 8.2 [0.8-89.3] vs. 35 yrs+ p=0.012) and participation in group sex in the last 3 months (AOR 3.0 [1.7-5.3], p<0.001). For women, rape was associated with selling sex in the past 3 months AOR 2.6 [1.0-6.6] p=0.048 and being HIV negative (AOR 4.8 [1.2-20.0] p=0.024.

Crude HIV incidence was higher among MSM reporting rape in the previous 3 months: IRR 5.7[1.8-18.0] p=0.003, but not when adjusted for behaviors common to both HIV and rape risk: AIRR 1.6 [0.5-5.2] p=0.458.



Incidence of first rape by gender and sexual orientation

Conclusions: Rates of rape among key populations in coastal Kenya are significant and events signal HIV risk for MSM. Multicomponent HIV prevention strategies for these populations should include immediate care pathways for victims of sexual abuse (including post-exposure prophylaxis). The impact of sexual assault upon mental health and prevention self-efficacy should be explored.

103LB Impact of the Ebola Epidemic on HIV Care in Macenta, Forest Guinea, 2014

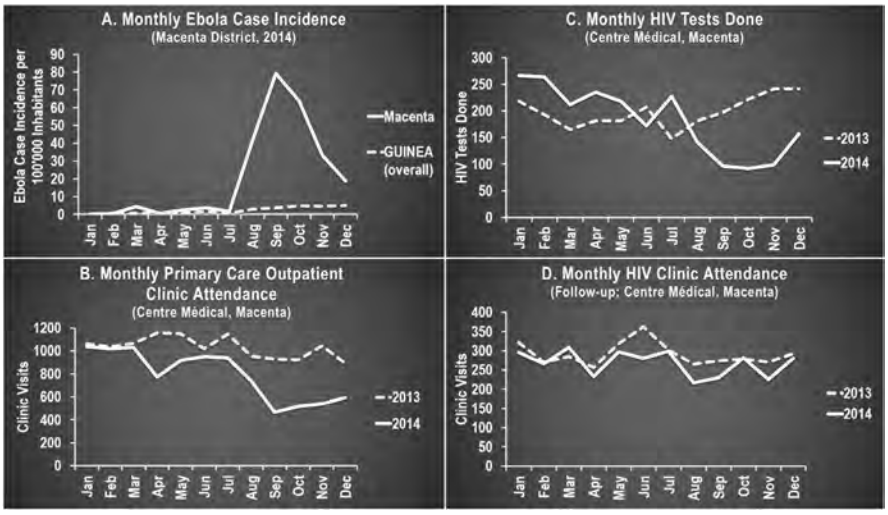
David Leuenberger[1]; Jean Hébélamou[1]; Stefan Strahm[1]; Gilles Wandeler[2]; Nathalie de Rekeneire[3]; François Dabis[3]
On behalf of International Epidemiological Databases to Evaluate AIDS - West Africa

[1]Mission Philafricaine, Conakry, Guinea; [2]Department of Infectious Diseases, University Hospital Bern, Bern, Switzerland; [3]Université Bordeaux, ISPED, Centre Inserm U897-Epidemiologie-Biostatistique, Bordeaux, France

Background: Macenta district (300,000 inhabitants) is one of the worst hit areas by Ebola virus in West Africa: cumulative incidence was 745 cases as of 12/31/2014 (250 cases/100'000, 10 times the country figure), and monthly incidence peaked at 79 cases/100'000 in September (Fig. A). The Centre Médical de Macenta, a public-private partnership between the Guinea Ministry of Health and the non-governmental organization Mission Philafricaine, offers general primary care services and runs the only HIV treatment center in the district. We assessed the impact of the ongoing epidemic on general/HIV care in Macenta.

Methods: We analyzed prospectively collected hospital data and linked them to Ebola surveillance data. Program indicators were compared between 2013 and 2014, with a focus on the epidemic period (August-December): overall use of hospital services, HIV services for new patients and for those already in care.

Results: No change in the availability of hospital services was reported throughout 2014; the catchment population was stable. Among the 60 hospital employees, there was one Ebola-related death (laboratory service) in 2014. Dispensation of antiretroviral drugs (ARV) increased by 26% from 2013 (N=675 patients in care) to 2014 (N= 780, of whom three are known to have died of Ebola). Yet there was a 40% drop in primary care outpatient clinic visits in August-December 2014 (ref. same period of 2013) (Fig. B), a 43% drop in out-of-pocket patient spendings (service fees and drug purchases), a 53% drop in newly diagnosed cases of tuberculosis, a 46% drop in HIV tests done (Fig. C), a 53% drop in patients newly diagnosed with HIV, and a 47% drop in HIV care enrolment. HIV follow-up dropped only by 11%, from 276 clinic visits per month in August-December 2013 to 247 for the same period of 2014. (Fig. D). Of the 185 patients newly enrolled in the first semester of 2014 (baseline median CD4 count 272/mm^3; IQR 106-457) 18.4% were lost to follow-up (LTFU) at six months during the epidemic period (def.: 30-day lateness after next scheduled visit). This LTFU 6-month indicator was 20.1% for the cohort of 204 patients enrolled in the first semester of 2013 (baseline CD4 count 230/mm^3; 84-410).



Ebola cases in Macenta district (A) and impact on primary care outpatient clinic attendance (B), HIV tests done (C) and HIV follow-up clinic attendance (D), all at the Centre Médical, Macenta

Conclusions: The Ebola epidemic resulted in a major drop in attendance of general outpatient services and thus in HIV testing and enrolment of new HIV+ patients, despite a continuous and unaltered service offer. We were however able to sustain HIV care for those already followed in this epidemic context.

103-ALB Favipiravir in Patients with Ebola Virus Disease: Early Results of the JIKI trial in Guinea

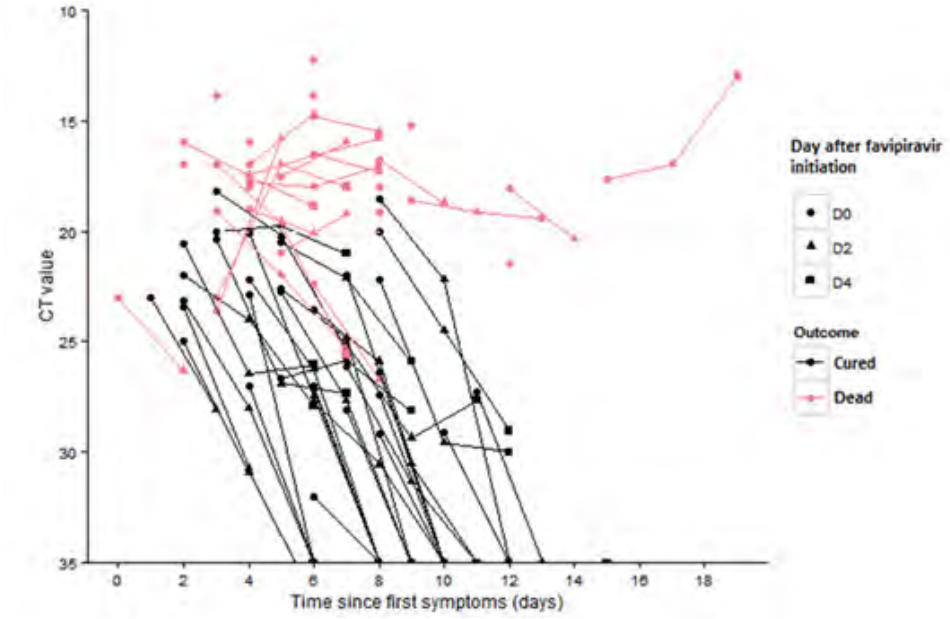
Daouda Sissoko[1], Elin Folkesson[2], M'lebing Abdoul[3], Abdoul Habib Beavogui[4], Stephan Gunther[6], Susan Shepherd[3], Christine Danel[1], France Mentre[5], Xavier Anglaret[1], **Denis Malvy**[1]

[1]Inserm U897, Université de Bordeaux, Bordeaux, France; [2]Médecins Sans Frontières, Bruxelles, Belgium; [3]ALIMA, Montreuil, France; [4]Centre de Formation et de Recherche en Santé Rurale de Maférinyah, Conakry, Guinée; [5]Inserm U738, Université Paris Diderot, Paris, France; [6]Bernhard-Nocht-Institut für Tropenmedizin, Hamburg, Germany

Background: The JIKI trial (Inserm C1463) assesses the benefits of high-dose favipiravir in reducing mortality and decreasing Ebola virus (EBOV) viral load in patients with Ebola virus disease (EVD).

Methods: JIKI is a phase II trial conducted in 2 Ebola treatment units run by MSF and ALIMA in Guinea. Inclusion criteria are: positive EBOV RT-PCR (Altona, crossing cycle threshold [CT] for positivity<40), age >1 year, ability to take oral drugs, and informed consent. Participants are prescribed oral favipiravir (adults: 6000mg Day [D]0 [H0 2400mg, H8 2400mg, H16 1200mg], and then 1200mg bid from D1 to 9). The primary endpoint is mortality. Mortality among participants is compared to mortality during the 3 month period preceding trial initiation in the same centers, as recorded in the MSF/EMLab database. On January 22, the DSMB recommended that the investigators present data on the first 69 adults and adolescents.

Results: from Dec 17, 2014 through January 20, 2015, 80 patients received favipiravir, including 69 adults and adolescents >14years (women 64%, mean age 38 years, median duration of illness 5 days). The baseline CT (BCT) was<20 in 42% and >20 in 58%; the baseline creatinine was >110 µM/L in 60% (BCT<20: 79%; BCT>20: 36%), including >300/µM in 27% (BCT<20: 43%; BCT>20: 10%); baseline ASAT level was >1000 IU in 38% (BCT<20: 77%; BCT>20: 17%); and baseline Creatine Kinase level >4000 IU in 18% (BCT<20: 24%; BCT>20: 8%). The figure shows the PCR CT values at baseline (D0) and at D2 and D4 following treatment initiation. Overall, 48% of participants died (BCT<20: 85%; BCT>20: 15%). The pre-trial mortality was 58% overall (p=0.15), 85% in patients with BCT<20 (p=0.26) and 30% in patients with BCT>20 (p=0.05). Mortality was 100% and 7% in patients with abnormal baseline creatinine values and BCT <20 or >20, respectively. The drug was well tolerated. Results of quantitative virology and PK tests will be available later.



Conclusions: In this non comparative proof of concept trial, most patients with CT< 20 had severe kidney failure and died, with no indication that favipiravir monotherapy improved survival. Patients with CT>20 had a lower mortality rate compared to pre-trial figures in the same settings. These preliminary data encourage continued testing of favipiravir with particular attention to identifying patients earlier in disease course, and to explore other therapeutic options, including combinations, in patients who present at advanced stages.

Session O-9 Oral Abstracts — Room 6D

10:00 am – 12:15 pm

New Insights Into HIV Persistence, Latency Reversal, and Viremia Rebound

104LB Durable Control of Viral Rebound in Humanized Mice by ABX464 Targeting Rev Functions

Noelie Campos[1]; Renier Myburgh[3]; Aude Garcel[1]; Audrey Vautrin[2]; Laure Lapasset[2]; Katjana Tantale[2]; Mark Wainberg[4]; Roberto Speck[3]; Didier Scherrer[1]; **Jamal Tazi**[2]

[1]ABIVAX, Montpellier, France; [2]University of Montpellier, Montpellier, France; [3]University of Zurich, Zurich, Switzerland; [4]McGill AIDS Center, Montréal, Canada

Background: Current therapies have succeeded in controlling AIDS pandemic. However, there is a continuing need for new drugs, in particular those acting through new and as yet unexplored mechanisms of action to achieve HIV infection cure. We took advantage of the unique feature of proviral genome to require both activation and inhibition of splicing of viral transcripts to develop molecules capable of achieving long lasting effect on viral replication through inhibition of rev-mediated viral RNA biogenesis

Methods: A dedicated library was designed and synthesized to modulate HIV RNA splicing (**WO2012080953, June 2012)** . The library was screened on infected PBMCs from healthy donors and ABX464 was selected.

Deep sequencing of viral RNA from treated cells established that ABX464 does not select for mutations, however, induced massive splicing of viral RNA.

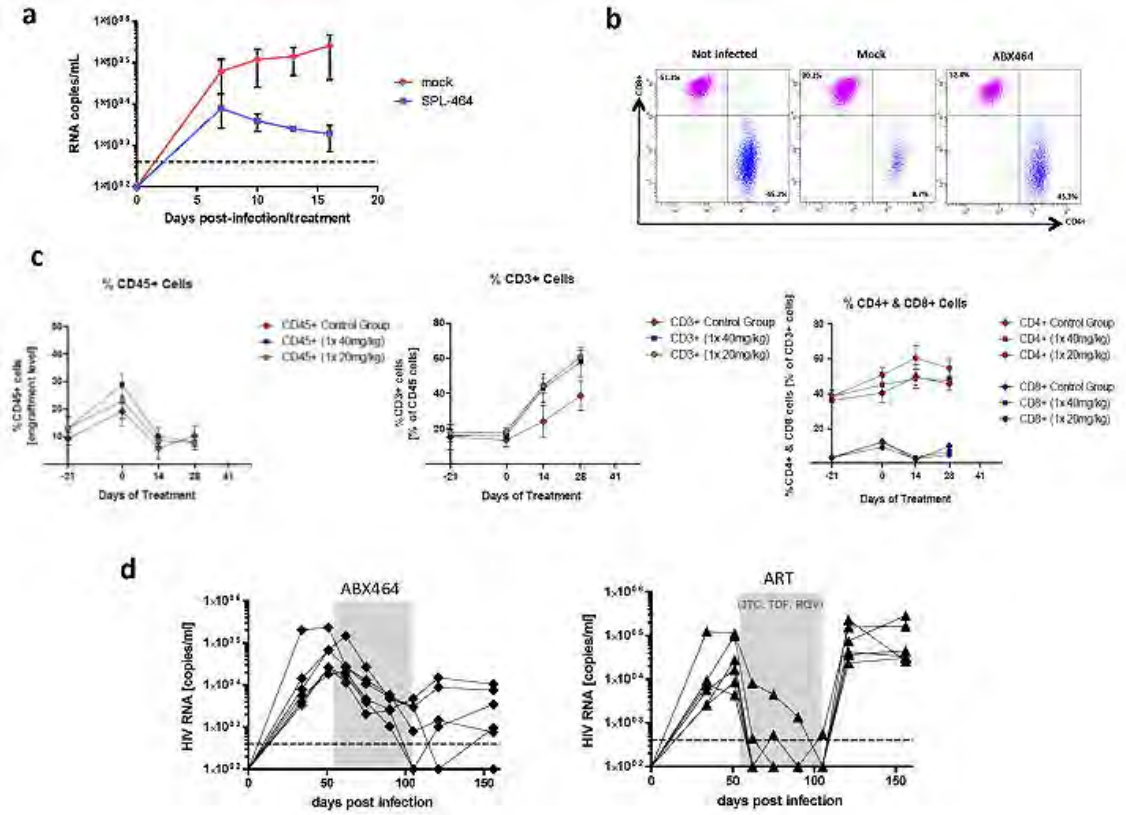
Using a system to visualize single HIV RNA molecules in living cells, we established that ABX464 interferes with Rev-mediated RNA biogenesis.

Two humanized mouse models were used to test the efficacy of ABX464 *in vivo;* SCID mice reconstituted with PBMCs and newborn NOG mice transplanted with CD34+ haematopoietic progenitor cells isolated from umbilical cord blood.

Results: ABX464 compromises HIV replication of clinical isolates of different subtypes without selecting for drug resistance in PBMCs or macrophages. ABX464 inhibits viral replication by preventing Rev-mediated export of unspliced HIV-1 transcripts to the cytoplasm. Retained viral RNA is massively spliced but normal cellular splicing is unaffected by the drug.

ABX464 alone, also efficiently compromised viral proliferation in two humanized mouse models infected with HIV that require a combination of 3TC, Raltegravir and tenofovir (ART) to achieve viral inhibition in current protocols. Crucially, there was no rebound of viral load for two months following treatment cessation of ABX464 whereas viral load increased dramatically just one week after ART treatment.

A phase I study conducted in healthy volunteers has demonstrated that a single administration of ABX464 was well tolerated up to 150 mg.



(a) Reconstituted SCID mice were infected with JRCSF HIV-1 strain by intraperitoneal injection. Control group received by gavage labrafil and 5% DMSO (n=15) and treated group 20mg/kg b.i.d of ABX464 in labrafil and 5% DMSO (n=14) for 15 days. (b) FACS analysis was performed on peritoneal wash at day 15 post-treatment to assess the CD8/CD4 ratio. (c) Engrafted NSG humanized mice were treated by oral gavage with ABX464 at either 20 mg or 40 mg/kg once a day for 30 days and indicated lymphocyte populations were monitored by FACS analysis. (d) NSG humanized mice were infected with the YU2 HIV-1 virus and treated either by oral gavage with SPL-464 at 40 mg/kg once a day for 30 days or by HAART (3TC-Tenofovir-Raltegravir and AZT).

Conclusions: ABX464 represents a novel class of anti-HIV molecules with unique properties. ABX464 has a long lasting effect in humanized mice and neutralizes the expression of HIV-1 proviral genome of infected immune cells including reservoirs and it is therefore a promising drug toward HIV cure.

105 Residual Viremia Caused by Clonally Expanded Tumor-Infiltrating CD4+ Cells

Francesco R. Simonetti[1]; Michele D. Sobolowski[2]; Shawn Hill[1]; Wei Shao[3]; Elizabeth Fyne[2]; Xiaolin Wu[1]; John M. Coffin[4]; Stephen H. Hughes[1]; John W. Mellors[2]; Frank Maldarelli[1]

[1]National Cancer Institute (NCI), Frederick, MD, US; [2]University of Pittsburgh, Pittsburg, PA, US; [3]Frederick National Laboratory for Cancer Research, Frederick, MD, US; [4]Tufts University, Boston, MA, US; [5]National Cancer Institute (NCI), Frederick, MD, US

Background: Clonal expansion of infected cells can contribute to HIV-1 persistence. We recently reported that a clonally-expanded population of HIV-infected cells was responsible for persistent viremia despite ART in a patient with metastatic squamous cell carcinoma (Maldarelli, et al., 2014). We conducted extensive ante- and post-mortem analysis of HIV-infected cells from this patient to investigate the organ and tumor distribution of this clonal variant.

Methods: Plasma and peripheral blood mononuclear cells (PBMC) were obtained ante mortem, and samples from spleen, ileum, rectum, 5 lymph nodes, and 5 tumor metastases were obtained at autopsy. Tissues were characterized by histo- and immunohistochemistry and qPCR of the genomic DNA was used to measure the levels of HIV *gag* sequences. A new single genome sequencing assay was performed to amplify the 800bp nef-U3 region from blood and tissues. Integration site flanking sequences were used to PCR amplify the full length of expanded proviruses. An ex-vivo infectious virus recovery assay was developed to characterize inducible HIV variants from PBMC-derived CD4+ cells. Sequences were subjected to phylogenetic and statistical analyses.

Results: HIV sequences (N=317) were recovered from plasma, PBMC, spleen, lymph nodes, and tumor tissues, which were infiltrated with both CD4+ and CD8+ T cells. In general, HIV variants were well mixed across blood and tissues and there was no evidence of localized replication. One provirus from a highly amplified clone (AMB-1), known to produce the majority of the HIV RNA detected in plasma, was enriched in tumor tissues. AMB-1 proviruses were present in each tumor metastasis, with an overall abundance in tumor tissue significantly (3.5-fold) greater than that detected in lymphoid tissues (p=0.0005). The full length AMB-1 sequence revealed an intact provirus and no drug resistance mutations. AMB-1 RNA was recovered in day 7 culture supernatants after stimulation (PHA, irradiated blasts) and co-culture of CD4+ T-cells with CD8-depleted allogeneic blasts but declined with continued culture associated temporally with outgrowth of other variants.

Conclusions: This study is the first report of residual viremia caused by an expanded cell carrying a specific intact HIV provirus. Cells from this clone accumulated specifically in cancer metastases. These observations suggest that immune stimuli, like tumor antigens, can contribute to cell expansion, and perhaps to the activation of the provirus and release of virions into plasma.

106 Analysis of HIV RNA in Single Cells Reveals Clonal Expansions and Defective Genomes

Ann Wiegand[1]; Jonathan Spindler[1]; Wei Shao[2]; Feiyu Hong[3]; Anthony R. Cillo[3]; Elias Halvas[3]; Elizabeth Fyne[3]; John M. Coffin[4]; John W. Mellors[3]; **Mary F. Kearney**[1]

[1]National Cancer Institute, Frederick, MD, MD, US; [2]Leidos, Frederick, MD, US; [3]University of Pittsburgh, Pittsburgh, PA, US; [4]Tufts University, Boston, MA, US

Background: Little is known about HIV-1 provirus expression in patients on suppressive ART. Characterizing cell-associated RNA (CAR) sequences in single cells can reveal their relationship to proviral populations and to persistent viremia. Here, we describe a new, sensitive method to assess the genetics of HIV CAR in viremic and virologically suppressed patients.

Methods: HIV-1 CAR was extracted from 4-6 separate aliquots of PBMCs from 3 patients using methods that were verified (by spiking known quantities of ACH2 cells into HIV negative PBMCs) to have high recovery of HIV-1 DNA and RNA. DNase-treatment and cDNA synthesis were optimized to ensure complete degradation of HIV DNA and high efficiency of long cDNA synthesis. Products were diluted to <1 HIV cDNA molecule/reaction, amplified, and sequenced (CAR-SGS). In patients who initiated ART with high HIV diversity, identical RNA sequences from the same aliquot of PBMCs were assumed to be derived from the same cell expressing HIV RNA, while identical sequences in different aliquots were assumed to be derived from clonally expanded, expressing cells. Single-genome sequences of proviral DNA and plasma HIV-1 RNA were compared to CAR sequences using standard bioinformatics methods.

Results: We developed and optimized methods for CAR-SGS to be used to profile cellular HIV-1 RNA expression in patients. 3 patients were studied: 1 was untreated and viremic and 2 were suppressed on ART. An average of 41 single cells per patient was analyzed. We found 53% of the HIV expressing cells in the viremic patient to be "high producers" (more than one RNA molecule detected) and 30% to be high producers in the suppressed patients. The diversity of the total RNA populations both before and during ART was ~1% in *pro-pol*, and G to A hypermutants were detected in the suppressed patients at similar levels to their proviral DNA populations (20% and 22%). We also detected HIV-1 expression from clonally expanded populations in one suppressed patient.

Conclusions: A new method to characterize the expression of HIV-1 proviruses that persist during ART reveals high levels of expression of RNA from infected individuals as well as clonally expanded cells. Further studies are needed to determine if HIV-1 expression results from spontaneous reactivation from latency or continuous low-level virus transcription and if these cells can be the source of viral rebound when ART is interrupted.

107 Low-Level HIV Viremias Originate in Part From Infected Proliferating Cells

Marta E. Bull[1]; Sherry McLaughlin[2]; Hannah Huang[2]; Sheila Styrchak[2]; Jaime Soria[3]; Eduardo Ticona[3]; Alberto La Rosa[4]; Caroline Mitchell[5]; James Mullins[1]; Lisa Frenkel[1]

[1]University of Washington, Seattle, WA, US; [2]Seattle Children's Research Institute, Seattle, WA, US; [3]Hospital Nacional dos de Mayo, Lima, Peru; [4]Investigaciones Médicas en Salud (INMENSA), Lima, Peru; [5]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [6]University of Washington, Seattle, WA, US

Background: Understanding mechanisms that allow HIV infection to persist despite suppressive antiretroviral therapy (**ART)** may help develop cure strategies. We observed that cells with HIV integrated into genes associated with cell proliferation or cancer form persistent clones, defined as multiple cells with identical proviruses (HIV *env* C2-V5) and with identical integration sites (**IS**). We hypothesized that these cell clones can produce virions, evident as low-level viremias (**LLV**).

Methods: A subset of HIV-infected ART-naïve subjects, enrolled into a 2-year observational study just before the initiation of nevirapine-based ART, were selected for this study based on detection of LLV (40-500 copies/mL) after one-year of suppressive (<40 copies/mL) ART. Samples were collected every 3 months over the 2 year study. HIV *env* (C2-V5) sequences were derived from peripheral blood mononuclear cells (**PBMC**) and plasma prior to starting ART and at a single LLV visit by single-genome-analysis (**SGA**). Multiple chromosomal IS and associated HIV *env* sequences were generated using an integration site looping assay (**ISLA**) (PMID25011556) from PBMC at the LLV visit that was diluted to a median single infected cell. IS were aligned using Bowtie and the location in the human genome determined using BLAT. HIV *env* sequences from LLV and PBMC were aligned with MUSCLE, and phylogenetic trees generated using DIVEIN. The proportion of LLV with *env* sequences identical to those in infected proliferating PBMC were evaluated by Fisher's exact test and distances from most recent common ancestor (**MRCA)** were evaluated by Wilcoxon signed rank test.

Results: Eight participants had LLV on 21/64 study visits. A median of 21 *env* sequences (range 19-28) were generated from a single LLV, and 90% were identical within a subject. A total of 287 IS sequences were generated from PBMC samples at the LLV visit (median 42 IS/subject, range 27-47). Proliferation of infected cells, evident from multiple cells with identical IS, was observed in 6/8 subjects. Two of these six subjects had proliferating clones with *env* sequences identical to those in LLV. Three of the six subjects with LLV sequences without linkage to proliferating PBMC had evidence of ongoing viral evolution, and hence continuing viral replication.

Conclusions: Clones of HIV-infected PBMC that persist during suppressive ART are capable of producing virions. LLV appear to originate from virion expression from proliferating infected cell clones or from low–level replication.

108 Treatment With a TLR7 Agonist Induces Transient Viremia in SIV-Infected ART-Suppressed Monkeys

James B. Whitney[1]; So-Yon Lim[1]; Christa E. Osuna[1]; Srisowmya Sanisetty[1]; Tiffany L. Barnes[2]; Peter T. Hraber[3]; Tomas Cihlar[2]; Romas Geleziunas[2]; Joseph Hesselgesser[2]

[1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US; [2]Gilead Sciences, Inc., Foster City, CA, US; [3]Los Alamos National Laboratories, Los Alamos, NM, US

Background: Latent reservoirs of replication competent HIV-1 persist in patients on antiretroviral therapy (ART) and represent the major obstacle to HIV eradication efforts. Considerable effort has been directed to identify pharmaceutical agents capable of safely reactivating latent HIV-1 in ART-suppressed patients.

Methods: A study was conducted in SIV-infected rhesus macaques (RM) on ART to determine if administration of an oral toll-like receptor 7 (TLR7) agonist would induce transient plasma viremia and reduce viral reservoirs. Ten RM were infected with SIVmac251 by rectal challenge. Plasma SIV RNA levels were measured by RT-PCR (limit of detection 50 copies/mL). The RM received ART at ~9 weeks post-infection (PI) and became virologically suppressed by 24 weeks PI; virologic suppression was maintained through week 45. At 45 weeks PI, 4 RM were administered 7 doses of the TLR7 agonist at twice monthly intervals, while on ART. The first 3 doses were 0.1, 0.2 and 0.3 mg/kg and the last 4 doses remained constant at 0.3 mg/kg. Total viral DNA was quantified in peripheral blood mononuclear cells (PBMC), colon and lymph node biopsies taken pre- and post-completion of TLR7 treatment. Two weeks after TLR7 dosing, ART was discontinued.

Results: The first 3 doses of TLR7 agonist administered to the SIV-infected ART-suppressed RM had limited effect on plasma viremia. However, doses 4 through 7 led to transient and consistent increases in plasma virus (500 - 1000 SIV RNA copies/mL) in all treated RMs with a return to < 50 copies/mL within 4-7 days of TLR7 dosing. After completion of the TLR7 regimen, SIV DNA levels were reduced by 56-75% in PBMC, colon and lymphoid tissues. Viral DNA levels remained unchanged in the placebo control RM. To determine if these transient plasma virus blips and decreases in viral DNA content also reduced the size of the viral reservoir, ART was discontinued. While the plasma virus rebound kinetics in animals dosed with the TLR7 agonist were comparable to the placebo group after discontinuation of ART, the TLR7 treated animals showed a ~0.5 $\log_{10}$ reduction in plasma virus setpoint as compared to the placebo group.

Conclusions: Multiple oral administrations of a TLR7 agonist in SIV-infected ART-suppressed RM was safe, induced transient plasma viremia, reduced viral DNA content in PBMCs, colon and lymphoid tissues and established lower viral setpoint after ART cessation. These novel findings support clinical investigation of a TLR7 agonist in HIV-1 infected patients on ART.

109 Panobinostat Broadly Activates Latent HIV-1 Proviruses in Patients

Kirston M. Barton[1]; Thomas A. Rasmussen[2]; Martin Tolstrup[2]; Wei Shao[4]; Bonnie Hiener[1]; Ajantha Solomon[3]; Lars Østergaard[2]; Sharon R. Lewin[3]; Ole Søgaard[2]; **Sarah E. Palmer**[1]

[1]Westmead Millennium Institute and University of Sydney, Westmead, Australia; [2]Aarhus University Hospital, Aarhus, Denmark; [3]Doherty Institute for Infection and Immunity, Melbourne, Australia; [4]National Cancer Institute, Rockville, MD, US

Background: To target the persistence of quiescent HIV-1 during ART, HDAC inhibitors have been used to induce viral transcription, which could potentially facilitate viral clearance. It is important that all replication competent proviruses are activated to fully purge infection. Therefore, we performed an in-depth analysis of the panobinostat clinical trial to determine whether the observed increases in unspliced cell-associated RNA (CA RNA) were due to transcription from a subset or a broad range of proviruses.

Methods: Panobinostat was administered to 15 patients on suppressive ART three times a week every other week for eight weeks (i.e., four cycles of drug). Cell-associated DNA (CA DNA) and RNA were extracted from PBMCs collected before, twice while receiving and four weeks after the final dose of panobinostat treatment. Additionally, plasma samples were collected prior to initiation of ART (nine patients) and during a post-panobinostat analytical treatment interruption (ATI, nine patients) to assess circulating HIV-1. Single-genome sequencing of the env region was used to characterise the virus from the cell-associated DNA and RNA and plasma RNA.

Results: The sequences obtained from the preART plasma reflected the infection status of the patient (acute vs. chronic). Phylogenetic analysis revealed that the panobinostat-induced viral RNA intermingled extensively with the CA DNA sequences from the equivalent time points, indicating that panobinostat activates transcription from a broad range of proviruses. The rebound virus from the ATI plasma was composed of expansions of homogenous sequences, and the sequences from this virus were genetically similar to the panobinostat-induced CA RNA sequences. Furthermore, CA DNA sequences that were identical to the rebound virus were detected. A significantly higher percentage of the sequences from the CA RNA were hypermutated compared to the CA DNA (p=0.04).

Conclusions: Panobinostat non-selectively activates transcription from quiescent proviruses in patients on suppressive ART, supporting its ability to activate HIV-1 from latency. Furthermore, panobinostat activated virus that was genetically similar to that observed during ATI, indicating that it targets virus that drives rebound following treatment discontinuation. The high percentage of hypermutated HIV CA RNA that was detected stresses the need for assays that measure replication competent virus when assessing latency reversing agents.

110LB The Size of the Active HIV Reservoir Predicts Timing of Viral Rebound

Behzad Etemad[1]; Hayat Ahmed[1]; Evgenia Aga[2]; Ronald Bosch[2]; John W. Mellors[3]; Daniel Kuritzkes[1]; Michael Para[4]; Rajesh T. Gandhi[5]; **Jonathan Li**[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]University of Pittsburgh, Pittsburgh, PA, US; [4]Ohio State University, Columbus, OH, US; [5]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

Background: Strategies to achieve sustained ART-free HIV remission will require validation in analytic treatment interruption (ATI) trials. Identifying virologic biomarkers that can predict time to viral rebound could accelerate the development of such therapeutics. We examined the association of pre-ATI cell-associated RNA (CA-RNA), DNA (CA-DNA), and residual viremia (RV) with timing of viral rebound during ATI.

Methods: We performed a retrospective combined analysis of participants from 5 ACTG studies who were virologically suppressed on ART and received no immunologic intervention prior to undergoing ATI. The timing of viral rebound was evaluated at either (1) confirmed viral load ≥200 HIV RNA copies/mL or (2) single viral load ≥1,000 HIV RNA copies/mL. Unspliced CA-RNA and CA-DNA were quantified using qPCR, and RV by the single-copy assay.

Results: Participants who initiated ART during acute/early infection (n=20) had lower levels of pre-ATI CA-RNA than those treated during chronic infection (n=104) (median <1.58 vs. 1.83 $\log_{10}$ HIV-1 RNA copies/10^6 PBMCs, P<0.01). No significant differences were seen in pre-ATI levels of CA-DNA or RV between those treated during acute/early vs. chronic infection. There were no significant differences by ART regimen (NNRTI vs. PI-based) in pre-ATI CA-RNA, CA-DNA, or RV. Higher pre-ATI CA-RNA levels were significantly associated with shorter time to viral rebound using a threshold of either 200 HIV-1 RNA copies/mL (≤4 wks [N=75] vs. 5-8 wks [N=35] vs. >8 wks [N=14]: 1.83 vs. 1.68 vs.<1.58 $\log_{10}$ HIV-1 RNA copies/10^6 PBMCs, Kruskal-Wallis P<0.01] or 1,000 HIV-1 RNA copies/mL (1.83 vs. 1.69 vs. <1.58 $\log_{10}$ HIV-1 RNA copies/10^6 PBMCs, P<0.01). The proportion of participants with detectable RV ≥1 copy/mL was significantly higher in those with shorter time to ≥200 HIV-1 RNA copies/mL (≤ 4 wks vs. 5-8 wks vs. ≥8 wks: 47% vs. 29% vs. 8%, Fisher's P=0.02]. No significant association was seen between CA-DNA levels and timing of viral rebound. A modest correlation was detected between levels of pre-ATI CA-RNA and CA-DNA (Spearman r=0.16, P=0.08).

Conclusions: The size of the active HIV reservoir, as reflected by levels of CA-RNA and RV, is associated with the time to viral rebound after interrupting ART. CA-RNA and RV have the potential to serve as biomarkers of efficacy for therapies aiming to achieve sustained ART-free HIV remission.

111LB Biomarkers to Predict Viral Rebound at Antiretroviral Therapy Interruption in SPARTAC

Jacob Hurst[1]; James Williams[1]; John P. Thornhill[2]; Matthew Pace[1]; Chris Willberg[1]; Elizabeth Hamlyn[3]; Abdel Babiker[4]; Rodney Phillips[1]; Sarah Fidler[2]; **John Frater**[1]
on behalf of the SPARTAC Trial Investigators

[1]University of Oxford, Oxford, United Kingdom; [2]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom; [3]King's College London, London, United Kingdom; [4]Medical Research Council Clinical Trials Unit, London, United Kingdom

Background: Treatment of HIV-1 infection with antiretroviral therapy (ART) in the first few weeks or months following transmission may induce a state of virological remission or 'post-treatment control' (PTC), in which viraemia remains suppressed when ART is stopped. We present an analysis of 18 immunological and virological biomarkers measured in primary HIV-1 infection (PHI) to determine if they may help predict PTC after treatment interruption (TI).

Methods: We retrospectively analysed a sub-group of samples from SPARTAC - a randomised controlled study of PHI incorporating a TI after 48 weeks of ART. We measured HIV-1 specific CD4 and CD8 T cell ELISpot responses, markers of T cell activation (HLA DR, CD38, CD25, CD69) and exhaustion (Tim-3, Lag-3, PD-1, TIGIT), soluble markers (Il-6, d-dimer), HIV-1 DNA (Total and Integrated), cell-associated unspliced RNA, CD4 count, plasma viral load and the CD4/CD8 ratio. Statistical analyses explored associations between biomarkers and Total HIV-1 DNA and time to viral rebound at TI, with measurements taken, where samples permitted, pre-therapy in all participants and at 48 weeks in those undertaking TI.

Results: We analysed 154 individuals prior to starting ART, a median of 73.8 days from the estimated date of seroconversion. 47 participants undertook a TI after 48 weeks of ART. In univariable regression models undertaken with samples from pre-therapy baseline, CD4/CD8 ratio, CD4 count, plasma viral load, CD8 CD38, CD8 PD-1, CD8 HLA DR, CD4 HLA DR, CD8 Lag-3 and d-dimer were significantly associated (all $P<0.05$) with HIV-1 DNA levels, but only CD4 count, viral load, CD8 CD38, CD8 Lag-3 and d-dimer survived in multivariable analyses.

When measured pre-therapy, and adjusting for levels of HIV-1 DNA, T cell exhaustion marker expression on CD4 (PD-1, Tim-3 and Lag-3) and CD8 (Tim-3 only) T cells predicted time to the return of viraemia (n=20; Table 1), but notably not when measured at TI. Apart from Total HIV-1 DNA, in this sub-group analysis we found no evidence for any other biomarkers associating with rebound when measured at baseline or at TI.

T cell	Biomarker	Association with time to rebound* (HR [CI]; p-value)
CD4+	PD-1	1.46 [1.06-1.85]; p=0.016
	Tim-3	1.36 [1.16-1.60]; p=0.009
	Lag-3	1.08 [1.02-1.15]; p=0.007
CD8+	Tim-3	1.15 [1.06-1.26]; p=0.001

Table 1: T cell exhaustion markers pre-therapy are associated with time to viral rebound at TI. *Multivariable Cox model adjusting for the biomarker and Total HIV-1 DNA. HR: Hazard ratio; CI: 95% confidence interval

Conclusions: In the search for an algorithm of biomarkers to help stratify treated PHI patients according to likelihood of PTC, these data indicate that pre-therapy measurements may be informative and that markers of T cell exhaustion should be included alongside HIV-1 DNA levels. This may also open critical new avenues for understanding the mechanisms underlying PTC, which need to be explored in larger cohorts.

112LB HIV-1 Diversity and Tropism of Rebound Virus After Treatment Discontinuation

Maria M. Bednar[1]; Blake Hauser[1]; Jeffrey M. Jacobson[2]; Ian Frank[4]; Joseph J. Eron[3]; Ronald Swanstrom[1]
On behalf of the NWCS 379 team

[1]University of North Carolina, Durham, NC, US; [2]Drexel University College of Medicine, Philadelphia, PA, US; [3]University of North Carolina, Chapel Hill, NC, US; [4]University of Pennsylvania, Philadelphia, PA, US

Background: Suppressive antiviral therapy has not been successful in eliminating virus, as patients on suppressive therapy retain a persistent, measurable, stable low-level viremia (LLV), and people discontinuing therapy see a rebound of virus from a persistent reservoir, as seen in the ACTG study A5068. ACTG study A5068 was designed to determine the efficacy of structured treatment interruptions and/or vaccination with an ALVAC-HIV vector for controlling viral replication after therapy discontinuation. Arm A (n=24) received neither STI nor vaccination, virologic rebound was detectable 2-4 weeks after discontinuation of therapy, and reached a peak several weeks later. We have used single genome amplification (SGA) of the viral *env* gene to assess genetic diversity followed by cloning to examine the tropism of the rebound virus by performing tropism assays to determine if the virus was adapted to grow in T cells (requiring high levels of CD4) or adapted to grow in macrophages (able to enter cells with low levels of CD4).

Methods: Viral RNA was isolated from the first available blood plasma sample containing viral load >1000 copies/mL from subjects infected with subtype B HIV-1 who had stopped therapy (10 total). We performed SGA to isolate individual *env* gene amplicons, 51 of which were cloned (average of 4 amplicons per tree) and infectivity analyzed at varying CD4 levels using Affinofile cells, in order to determine the viral entry phenotype for CD4 usage.

Results: Phylogenetic analysis of the viral *env* genes showed low diversity in each subject, consistent with an initially clonal repopulation of the viral population during rebound. No evidence of macrophage-tropic virus was found meaning that all of the rebound *env* genes tested encoded proteins that required high levels of CD4 for efficient entry of pseudotyped virus into Affinofile cells.

Conclusions: The source of the rebound virus is poorly understood, with the current model assuming this virus comes from resting CD4+ T cells; however, other cell types could be the source of this virus. Our analysis further excludes a myeloid cell source, where virus was persistently infecting these cells prior to therapy. Such a virus would have adapted to be able to use low levels of CD4, and this type of virus was not detected as the rebound virus. While our analysis does not identify the cell type harboring the virus that initiated the rebound, it is consistent with a CD4+ T cell as the source of the virus.

Themed Discussion Abstracts

188 HIV-1 Exploits CD169 to Evade IFNα-Induced Antiviral State in Myeloid Cells

Hisashi Akiyama[1]; Nora Ramirez[1]; Gregory Gibson[2]; Simon Watkins[2]; Zandrea Ambrose[2]; Rahm Gummuluru[1]

[1]Boston University School of Medicine, Boston, MA, US; [2]University of Pittsburgh School of Medicine, Pittsburgh, PA, US; [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, US

Background: A hallmark of HIV-1 infection in vivo is chronic immune activation concomitant with type I interferon (IFN-I) production. Although IFN-Is induce an antiviral state in many cell types, HIV-1 can replicate even in the presence of IFN-Is in vivo. We have recently identified the IFN-I-inducible protein CD169 as an HIV-1 receptor on myeloid dendritic

cells that can mediate robust infection of $CD4^+$ T cells in trans. Since CD169 expression is also induced by IFN-Is on macrophages, we hypothesized that CD169 induced by IFN-I could facilitate productive HIV-1 infection in macrophages in cis and thus offset antiviral effects of IFN-Is.

Methods: To investigate the effect of IFN-Is on HIV-1 replication in myeloid cells, a monocyte cell line, THP-1 or primary monocyte-derived macrophages (MDMs) were treated with IFNα for 48 hours and infected with HIVΔenv-luc reporter virus pseudotyped with HIV-1 Lai (HIV/Lai) or VSV-G (HIV/G) glycoproteins, or replication competent HIV-luc. HIV-1 fusion was measured by the conventional Vpr-BlaM assay. To investigate if $CD169^+$ myeloid cells are productively infected in vivo, lymph nodes (LNs) from pigtailed macaques chronically infected with RT-$SHIV_{mne027}$ were stained for $p27^{gag}$ and CD169.

Results: As reported previously, HIV/G infection was severely attenuated in IFN-treated-THP-1. Surprisingly, however, replication of HIV/Lai was enhanced in IFN-treated-THP-1 than in untreated THP-1. We found that HIV/Lai fusion was greatly enhanced in IFN-treated-THP-1, while that of HIV/G was severely attenuated. This enhanced fusion and infection depended on CD169 since pretreatment with αCD169 blocking antibody abrogated the enhancement of virus fusion and replication in IFN-treated-THP-1. IFNα treatment of MDMs also up-regulated CD169 and HIV-1 fusion in treated MDMs was enhanced (2-fold) in a CD169-dependent manner. Interestingly, CD169 enhanced virus replication in MDMs even in the presence of IFNα (>2-fold higher compared to MDMs pretreated with αCD169 blocking antibody). Finally, LNs from SHIV-infected macaques showing signatures of immune activation contained more $CD169^+$ cells than those of uninfected animals and, intriguingly, a large proportion of $p27^{gag+}$ cells were also $CD169^+$.

Conclusions: These studies suggest that HIV-1 has exploited CD169 to attenuate IFN-I-induced antiviral state in myeloid cells.

192 HIV and SIV Inhibition by RNA-Associated Early Stage Antiviral Factor (REAF)

Aine McKnight
Queen Mary University of London, London, United Kingdom

Background: The interaction of viruses with their human host is a constant war. The discovery of novel anti-viral restriction factors illuminates unknown aspects of innate sensing and immunity.

Methods: An siRNA screen of ~20,000 human genes was used to uncover those involved in inhibition of HIV replication. We identified RNA-associated Early-stage Anti-viral Factor (REAF) as an inhibitor of HIV replication

Results: 114 genes were identified to be potentially involved in intrinsic resistance. Focusing on the most potent factors led us to REAF. REAF (previously RPRD2) was annotated in the human genome but with no known function. We observed more than 50 fold rescue of HIV-1 infection following knockdown of REAF by specific siRNA. Quantitative PCR was used to measure the effect of REAF knockdown on two steps in the replication cycle – production of reverse transcripts and integration of viral cDNA. Both steps were strongly enhanced. Conversely, when REAF is over expressed in target cells fewer reverse transcripts are produced. Human REAF can also inhibit HIV-2 and simian immunodeficiency virus (SIV) infection. REAF interacts (either directly or indirectly) with HIV RNA or RNA:DNA intermediates during reverse transcription. Also, during the process of reverse transcription REAF protein is degraded, within one hour of infection, in a proteosomal dependent manner.

Furthermore, REAF can inhibit HIV replication via different routes of entry into cells. Its potency is, however, highly dependent on the pathway of entry used and we show it is the lentiviral restriction factor 2 (Lv-2) [1,2].

Conclusions: We propose that REAF is part of an anti-viral surveillance system destroying incoming retroviruses. This novel mechanism could apply to invasion of cells by any intracellular pathogen.

1 Marchant, D., Neil, S. J., Aubin, K., Schmitz, C. & McKnight, A. An envelope-determined, pH-independent endocytic route of viral entry determines the susceptibility of human immunodeficiency virus type 1 (HIV-1) and HIV-2 to Lv2 restriction. *J Virol* **79**, 9410-9418, (2005).

2 Schmitz, C., Marchant, D., Neil, S. J., Aubin, K., Reuter, S., Dittmar, M. T. & McKnight, A. Lv2, a novel postentry restriction, is mediated by both capsid and envelope. *J Virol* **78**, 2006-2016, (2004).

184 Regulation of the Innate Immune Sensing of HIV by the Viral Capsid and the Cytosolic DNA Sensor cGAS

Nicolas Manel
Institut Curie, Paris, France

Background: Dendritic cells (DCs) play an important role in the detection of viral infections through innate sensing pathways and the induction of immune responses. The pathogenic virus HIV-1 escapes cytosolic innate immune sensing by monocyte-derived DCs. Innate sensing of HIV-1 by DCs can be rescued by complementing the virus with the small protein Vpx found in HIV-2, attributing the lack of cytosolic sensing of HIV-1 to to the poor ability of the virus to replicate in MDDCs as a result of the SAMHD1 restriction. In contrast, VSV-G-pseudotyped HIV-2 efficiently infects MDDCs and activates pathways of innate immunity. HIV-2 is much less pathogenic than HIV-1, suggesting that such recognition by DCs may be important for effective anti-HIV immune responses. However, the mechanism of cytosolic HIV sensing by DCs remained to be determined.

Methods: Initial experiments showed that the viral capsid and its interaction with the cellular protein Cyclophilin A plays an important role. To study HIV sensing, we designed mutations in capsid to increase its affinity for Cyclophilin A (HIVac).

Results: Strikingly, HIVac mutated viruses maintained the ability to activate DCs but had lost the ability to infect the DCs. Using such virus, we found that innate sensing requires synthesis of the viral cDNA, but not nuclear entry and genome integration. We also find that the wild-type HIV-1 capsid normally shields the cDNA before genome integration, preventing its detection by innate sensor(s). Finally, we examined cytosolic DNA sensors using RNAi. We find that the cytosolic DNA sensor cGAS (cyclic GMP-AMP synthase) is required for innate recognition of HIV-1 and HIV-2 cDNA by DCs.

Conclusions: Altogether, these results establish that cGAS is an important innate sensor of HIV-1 and HIV-2 and uncover an essential regulation of this sensing mechanism by capsid and Cyclophilin A. We are currently investigating various aspects of these innate immune mechanisms and new findings will be presented.

203 Mapping Vpx and Vpr Specificity in Antagonism of SAMHD1

Chelsea Spragg; Michael Emerman
Fred Hutchinson Cancer Research Center, Seattle, WA, US

Background: The lentiviral accessory protein Vpx enhances infectivity of macrophages, dendritic cells, and resting T-cells by inducing degradation of the restriction factor SAMHD1, which blocks replication at reverse transcription. Vpx bridges SAMHD1 to the host ubiquitin ligase substrate receptor DCAF1, leading to polyubiquitination of SAMHD1 and degradation by the proteasome. The *vpx* gene is present in only two major lineages of lentivirus including HIV-2, but the paralagous *vpr* is present in all extant lineages. In certain cases, Vpr also has the ability to degrade host SAMHD1. SAMHD1 has evolved under positive selection due to viral antagonism, resulting in species-specificity between host SAMHD1 and viral Vpx/r. Depending on the lineage, Vpx exclusively targets either the N-terminus or the C-terminus of SAMHD1; however, the regions of Vpx/r controlling specificity

are unknown. The structure of SIVmac Vpx bound to DCAF1 and the C-terminus of SAMHD1 has been solved, but there is extreme sequence diversity in *vpr* and *vpx* from divergent viruses.

Methods: We used an evolutionary and structural approach to find appropriate and robust breakpoints in Vpx and Vpr in order to create functional, chimeric viral proteins. By assaying for the gain of ability to degrade resistant SAMHD1, these chimeric proteins assisted in mapping of determinants of specificity in Vpx and Vpr from several lentiviral lineages.

Results: We found that the majority of residues involved in binding DCAF1 were conserved in essentially all SAMHD1-degrading Vpx and Vpr. We identified highly conserved amino acids flanking the regions of SIVmac Vpx involved in binding SAMHD1. These conserved motifs served as breakpoints to create chimeric proteins between Vpr and Vpx from SIVs infecting macaque, red-capped mangabey, and African green monkeys. We were then able to retarget Vpx and Vpr from different lentiviruses to degrade heterologous SAMHD1. Depending on the lineage, the specificity of Vpx/r in degrading SAMHD1 maps to one or two regions in the viral protein.

Conclusions: The structure of Vpx and Vpr proteins and their interaction with the host ubiquitin ligase is widely conserved, despite high levels of sequence variation across lineages. Given the evolutionary constriction in maintaining this ubiquitin ligase binding, similar regions of Vpr/x are used to target SAMHD1, allowing the mapping of sites that govern SAMHD1 antagonism in species-specific interactions.

202 A Surprising New Function of SAMHD1 as a Pro-Pathogenic Factor in HIV Infection

Gilad Doitsh; Nicole Galloway; Xin Geng; Isa Monus Arias; Zhiyuan Yang; Warner C. Greene

The J. David Gladstone Institute, University of California San Francisco, San Francisco, CA, US

Background: Depletion of CD4 T cells and development of chronic inflammation are signature processes in HIV pathogenesis that propel disease progression. Due to endogenous SAMHD1 restriction activity in quiescent lymphoid CD4 T cells, the viral chain elongation phase of reverse transcription is attenuated, giving rise to incomplete cytosolic DNA transcripts. CD4 T-cell death is triggered after sensing of these cytosolic DNA intermediates by interferon gamma Inducible protein 16 (**IFI16**). Death occurs following caspase-1 activation in inflammasomes and the induction of **pyroptosis**, a highly inflammatory form of programmed cell death. These findings mechanistically connect CD4 T-cell death and chronic inflammation––the two signature pathogenic processes of active HIV infection.

Methods: Human lymphoid aggregated cultures (HLACs) prepared using tonsil and spleen, and lymph node biopsies from consenting HIV-infected volunteers were used.

Results: We now show that SAMHD1 restriction activity influences how CD4 T cells die. Degradation of SAMHD1 by Vpx encoded by HIV-2 thwarts abortive infection in resting, non-permissive lymphoid CD4 T cells redirecting the cell death pathway away from caspase-1-mediated pyroptotic pathway (inflammatory) toward caspase-3-mediated apoptotic pathway (noninflammatory). SAMHD1 effectively suppresses caspase-1 activation and pyroptosis when infection occurs with cell-free virions. However, in the context of cell-to-cell transmission, which is 100-1,000-fold more efficient, SAMHD1 restriction is only partially effective resulting in the accumulation cytoplasmic viral DNA. This DNA is sensed by IFI16 resulting in caspase-1 activation and triggering of the pyroptotic death pathway. The action of other cellular factors like TREX1 and SLX4 (single and double strand DNA nucleases) may require further increase in the levels the cytosolic DNA needed to trigger pyroptosis.

Conclusions: 1. The Vpx protein thwarts inflammatory pyroptosis following HIV-2 infection by degrading SAMHD1 thereby avoiding abortive infection and sensing of cytosolic viral DNA.

2. SAMHD1 is a bifunctional host factor capably restricting infection of resting CD4 T cells by cell-free HIV virions but functioning as a pro-pathogenic factor when resting CD4 T cells are infected by HIV-1 by the cell-to-cell route.

191 Characterization of the Activity of an Innate Immunity Protein, the Apolipoprotein L6

Nitisha Pyndiah[1]; Angela Ciuffi[1]; Amalio Telenti[2]

[1]*Institute of Microbiology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland;* [2]*J Craig Venter Institute, San Diego, CA, US*

Background: Host restriction factors are proteins hampering virus replication, and share common features including positive selection, viral counteraction, interferon-inducible expression and differential expression among HIV+ patients. APOL6 was identified in a screen aiming at identifying novel HIV-1 candidate host restriction factors. Another member of the APOL family, APOL1, has been previously described for its protective role against the parasite *Trypanosoma brucei* and more recently as a new HIV restriction factor (Taylor *et al.*, 2013). The aim of the study was to characterize the activity of APOL6.

Methods: We evaluated the ability of APOL6 primate orthologues, chimeras and mutants to inhibit the GFP expression from an HIV-1 based genomic vector in co-transfection experiments. We also assessed the impact of APOL6 on transduction of reporter viruses. Analysis was carried out using flow cytometry

Results: APOL6-mediated restriction was validated in a co-transfection assay with an HIV-1 LTR-EF1-GFP, showing up to 10-fold reduced GFP expression in APOL6-expressing cells compared to control cells. Species-specific restriction of APOL6 primate orthologs co-transfected with HIV-1 LTR-EF1-GFP revealed a higher GFP inhibition mediated by hominids and new world monkey APOL6 compared to old world monkeys APOL6. A similar APOL6-mediated inhibition was observed when APOL6 was co-transfected with alternate GFP expression vectors. In contrast, APOL6 was not able to restrict HIV-based vector transduction nor adenovirus or LCMV. Furthermore, APOL1 and APOL3 constructs were also tested in co-transfection and transduction experiments and followed the same tendency as APOL6. Through co-transfection analyses using human and rhesus APOL6, respectively displaying high and low inhibition ability, we identified a specific APOL6 domain and residue mediating APOL6 effects.

Conclusions: All together, these data suggest that APOL6-mediated activity is not virus-specific, but rather displayed a broad action against various promoter constructs. This points out to a specific APOL6 mechanism, potentially acting at the level of nucleic acid (DNA or RNA) sensing and/or degradation. APOL6 domain and residue responsible for the activity was identified. The mechanism used by APOL6 is very likely to be shared by other members of the family. We are currently identifying APOL6 cellular interactants by Mass spectrometry to elucidate the mechanism of APOL6-mediated restriction.

531 Pharmacokinetic Interactions Between Antidiabetics and Efavirenz Using PBPK Modeling

Catia Marzolini[1]; Rajith Rajoli[2]; Luigia Elzi[1]; Manuel Battegay[1]; David Back[2]; Marco Siccardi[2]

[1]*University Hospital Basel, Basel, Switzerland;* [2]*Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom*

Background: Diabetes has emerged as an important co-morbidity in the aging HIV population. The management of diabetes is complicated by the issue of drug-drug interactions (DDI) between antidiabetics and antiretroviral drugs and the lack of clinical data on how to manage these DDI. The antidiabetics pioglitazone (PIO) and repaglinide (REP) are metabolized by CYP2C8 and CYP3A4 and therefore are subject to DDI with efavirenz (EFV), an inducer of CYP3A4 and inhibitor of CYP2C8. The objective of this study was to simulate the pharmacokinetic (PK) interaction between PIO or REP and EFV using physiologically based pharmacokinetic (PBPK) modeling.

Methods: *In vitro* data describing the physicochemical properties, absorption, distribution, metabolism and elimination of PIO, REP and EFV, as well as the CYP induction and inhibition potential of EFV were obtained from published literature. The experimental data were integrated in a PBPK model developed using Simbiology (Matlab, R2013b),

representing molecular, physiological and anatomical processes defining PK. PIO, REP and EFV plasma profiles were simulated in 50 virtual individuals receiving either PIO 15 mg once daily (QD) or REP 2 mg thrice daily (TID) with or without EFV 600 mg QD for 14 days. Dose adjustments of PIO and REP were simulated to overcome the DDI with EFV.

Results: Simulated PK parameters were in agreement with observed clinical data. Simulated versus observed mean AUC and Cmax (± SD) were: 3699 (1413) vs 5020 (1070) ng.h/ml and 535 (80) vs 597 (115) ng/ml for PIO; 50 (16) vs 69 (78) ng.h/ml and 21 (5) vs 48 (32) ng/ml for REP; 92931 (44533) vs 58089 (23046) ng.h/ml and 6158 (1855) vs 4072 (1168) ng/ml for EFV. The geometric mean ratios with 90% confidence interval (GMR, 90% CI) of PIO or REP with and without EFV are presented in the table. An increase in PIO and REP dosage to 22.5 mg QD and 4 mg TID, respectively, was predicted to be sufficient to overcome EFV induction.

Drug	PK parameter	GMR	90% CI
Pioglitazone	AUC	0.53	0.46-0.60
	Cmax	0.77	0.73-0.80
Repaglinide	AUC	0.47	0.42-0.52
	Cmax	0.50	0.45-0.56

Conclusions: The prediction of DDI for drugs whose metabolism is concurrently induced and inhibited can be complex. The developed model, integrating both concurrent effects on CYPs and temporal changes in drug concentrations, shows that EFV has mainly an inducing effect on PIO and REP metabolism. PBPK modeling represents a useful tool to predict complex DDI as often encountered in multimorbid elderly HIV-infected patients and to support the design of prospective clinical trials.

532 In Silico Simulation of Interaction Between Rifampicin and Boosted Darunavir

Marco Siccardi; Owain Roberts; Rajith Rajoli; Laura Dickinson; Saye Khoo; Andrew Owen; David Back

University of Liverpool, Liverpool, United Kingdom

Background: The optimization of antiretroviral regimens in HIV-infected patients co-administered with anti-TB drugs is challenging since rifampicin (RIF), a principal element of the anti-TB therapy, is a strong inducer of key metabolic enzymes. Physiologically-based pharmacokinetic (PBPK) modelling represents an innovative approach to simulate clinical scenarios in the absence of clinical data, by integrating *in vitro* data in mathematical models. The aim of this research was to develop a PBPK model for the co-administration of ritonavir-boosted darunavir (DRV/r) and RIF and predict optimal dosing strategies to overcome the drug-drug interaction (DDI).

Methods: *In vitro* data describing physicochemical properties, absorption, distribution, metabolism and elimination (ADME) of DRV, ritonavir (RTV) and RIF, as well as the inhibition and induction potential of RTV and RIF were determined experimentally or obtained from the literature. A PBPK model was developed integrating experimental *in vitro* data in algorithms representing molecular, physiological and anatomical processes defining ADME. The PK of DRV/r and RIF was simulated in 100 virtual individuals. The impact of RIF (600mg *qd*) on DRV/r was determined and DRV and RTV *qd* and *bid* dose adjustments were simulated.

Results: Simulated DRV/r pharmacokinetic parameters were (mean ± SD) C_{trough} (2.02 ± 1.17 μg/ml), C_{max} (8.23 ± 1.73 μg/ml) and AUC (115.6 ± 32.9 μg/mL.h), which is in agreement with observed PK data for DRV/r 800/100 mg qd in HIV-infected patients: C_{trough} (2.11 ± 1.22 μg/ml), C_{max} (6.75 ± 1.68 μg/ml) and AUC (75.62 ± 26.44 μg/mL.h). The simulated effect of RIF on DRV exposure resulted in a decrement of 57.7% for AUC, 79.5% for C_{trough} and 34.6% for C_{max}. The effect of RIF was overcome by increasing the DRV/ r dose to 1600/200 mg *qd* or 800/100 mg *bid* (Table 1).

Table 1 Ritonavir-Boosted DRV dose adjustments (+RIF) and simulated effect on (mean ± SD) AUC_{24hr} compared to reference dosing (800/100 *qd* - RIF)

qd regimen + RIF	% of AUC_{24hr} compared to reference dosing (800/100 *qd* - RIF)	*bid* regimen + RIF	% of AUC_{24hr} compared to reference dosing (800/100 *qd* - RIF)
800/100	42 ± 18	600/100	89 ± 32
800/150	51 ± 21	600/150	93 ± 33
800/200	58 ± 26	600/200	98 ± 35
1200/100	66 ± 29	**800/100**	**118 ± 43**
1200/150	77 ± 30	**800/150**	**127 ± 44**
1200/200	83 ± 31	**800/200**	**142 ± 58**
1600/100	89 ± 43	**1200/100**	**171 ± 80**
1600/150	99 ± 53	**1200/150**	**186 ± 93**
1600/200	**111 ± 54**	**1200/200**	**197 ± 101**

Conclusions: The developed PBPK model predicted the in vivo pharmacokinetics of DRV/r and the interaction with RIF. Based on these findings, a DRV/r regimen of 1600/200 mg *qd* or 800/100 mg *bid* could mitigate the effect of RIF on DRV/r PK. Mechanistic evaluation of ADME can inform PBPK models and prediction of interaction between drugs. PBPK may be particularly helpful for the rational design of clinical trials evaluating dose adjustment strategies to overcome DDIs in patients concomitantly receiving antiretrovirals and anti-TB drugs.

533 Pharmacogenetics of Pregnancy-Induced Changes in Efavirenz Pharmacokinetics

Adeniyi Olagunju[1]; Oluseye Bolaji[2]; Alieu Amara[1]; Laura Else[1]; Ogechi Okafor[3]; Ebunoluwa Adejuyigbe[2]; Oyigboja Johnson[4]; David Back[1]; Saye Khoo[1]; Andrew Owen[1]

[1]University of Liverpool, Liverpool, United Kingdom; [2]Obafemi Awolowo University, Ile-Ife, Nigeria; [3]Bishop Murray Medical Centre, Makurdi, Nigeria; [4]Catholic Caritas Foundation of Nigeria, Makurdi, Nigeria

Background: Physiological changes during pregnancy coupled with single nucleotide polymorphisms (SNPs) in drug disposition genes are known to alter the pharmacokinetics (PK) of many drugs. In the present study the magnitude of pregnancy-induced changes in efavirenz (EFV) PK in genetically-defined subgroups was investigated.

Methods: This was an observational study with an enrichment design conducted in two phases. In the preliminary phase, we explored associations between selected *CYP2B6*, *NR1I3*, *CYP2A6*, and *ABCB1* SNPs and mid-dose EFV concentrations in an unselected cohort of HIV positive women during pregnancy and postpartum. In the second phase, patients were stratified according to *CYP2B6* 516G>T (rs3745274). Accordingly, randomly selected patients in each genotype group were invited for the intensive PK phase; samples were collected at 0.5, 1, 2, 4, 8, 12 and 24 hours after an observed evening dose of EFV.

Results: A total of 211 HIV positive women taking EFV-based regimens for prevention of mother-to-child transmission (PMTCT) of HIV during pregnancy (n = 77) or postpartum (n = 134) were recruited. Of the nine SNPs investigated, only *CYP2B6* 516G>T was independently associated with EFV plasma concentrations during both pregnancy and postpartum and was used to pre-select patients for the intensive PK phase. A global comparison showed a 42.6% increase in CL/F ($p = 0.02$), 29.8% reduction in AUC_{0-24} ($p = 0.02$) and 50.7% reduction in C_{min} ($p = 0.01$) during pregnancy compared with postpartum. The median (range) C_{min} was 1000 ng/ml (429-5190) and the change in C_{max} was not statistically significant ($p = 0.07$). However, when stratified for *CYP2B6* 516G>T status, EFV CL/F increased by 100% during pregnancy compared with postpartum ($p = 0.001$) in patients with

the *CYP2B6* 516GG genotype. The AUC_{0-24}, C_{max} and C_{min} were reduced by 50.6% ($p = 0.001$), 17.2% ($p = 0.14$) and 61.6% ($p = 0.003$) during pregnancy, with values of 25,900 ng.hr/ml (21,700-32,600), 2640 ng/ml (1260-3490) and 592 ng/ml (429-917), respectively (Table 1).

Table 1. EFV pharmacokinetic parameters* during pregnancy and postpartum based on *CYP2B6<i/> 516G>T genotypes.*

	Clearance/F (L/hr)	AUC_{0-24} (ng.hr/ml)	C_{max} (ng/ml)	C_{min} (ng/ml)
All (CYP2B6 516GG, GT and TT)				
Pregnancy (n = 25)	14.1 (2.96-27.7)	42,600 (21,700-203,000)	3490 (1260-14400)	1000 (429-5190)
Postpartum (n = 19)	9.89 (3.39-20.7)	60,700 (29,000-177,000)	4850 (2050-9760)	2030 (755-6740)
Pregnancy vs Postpartum: % change	42.6	-29.8	-28.0	-50.7
p value	0.023	0.023	0.072	0.012
CYP2B6 516GG				
Pregnancy (n = 8)	23.2 (18.4-27.7)	25,900 (21,700-32,600)	2640 (1260-3490)	592 (429-917)
Postpartum (n = 6)	11.6 (9.37-18.4)	52,400 (32,600-64,000)	3190 (2700-3800)	1540 (867-2310)
Pregnancy vs Postpartum: % change	100	-50.6	-17.2	-61.6
p value	0.0013	0.0013	0.14	0.0027
CYP2B6 516GT				
Pregnancy (n = 14)	13.7 (2.96-23.3)	43,900 (25,700-203,000)	3660 (2490-14400)	1120 (571-5190)
Postpartum (n = 7)	11.9 (4.71-20.67)	50,700 (29,000-128,000)	4850 (2050-6780)	1520 (755-4860)
Pregnancy vs Postpartum: % change	15.1	-13.4	-24.5	-26.3
p value	0.85	0.85	0.43	0.63
CYP2B6 516TT				
Pregnancy (n = 3)	6.83 (5.22-8.15)	87,900 (73,700-115,000)	5770 (5320-5950)	2890 (2660-4030)
Postpartum (n = 6)	4.69 (3.39-5.35)	129,000 (112,000-177,000)	6940 (6370-9760)	5130 (3830-6740)
Pregnancy vs Postpartum: % change	45.6	-31.9	-16.9	-43.7
p value	0.095	0.095	0.024	0.048

*Values are presented as median (range) and *p<i/> values are for Mann-Whitney U test.*

Conclusions: The clinical relevance of these findings is uncertain, since dose-reduction of EFV in non-pregnant adults was previously not associated with increased risk of virological failure. Nevertheless, the impact of pharmacogenetic variability on mother-to-child transmission of HIV should be further studied.

534 Antiretroviral Drug Transporters and Metabolic Enzymes in Human Testicular Tissue

Billy Huang[1]; Md. Tozammel Hoque[1]; Mohammad-Ali Jenabian[3]; Kishanda Vyboh[2]; Nancy Sheehan[2]; Pierre Brassard[4]; Maud Bélanger[4]; Nicolas Chomont[5]; Jean-Pierre Routy[2]; Reina Bendayan[1]

[1]University of Toronto, Toronto, Canada; [2]McGill University, Montréal, Canada; [3]Université du Québec à Montréal, Montréal, Canada; [4]Metropolitan Centre of Plastic Surgery, Montréal, Canada; [5]Vaccine and Gene Therapy Institute of Florida, Port St Lucie, FL, US

Background: Previous studies have reported that HIV-1 is capable of both acute and persistent infection in the testes. The naturally restrictive environment in the testes due in part to the blood-testes-barrier (BTB), suggests that this barrier could restrict antiretroviral (ARV) penetration into this tissue and contribute to the formation of a viral sanctuary. This study aims to characterize drug transporters and metabolic enzymes expression and localization in the testes of uninfected and HIV-1-infected men receiving antiretroviral therapy (ART) in order to gain further insight on the factors regulating ARV disposition in this organ.

Methods: Testicular tissues were collected from uninfected men (N=8) and HIV-1 infected men on ART (plasma viral load <50 copies/mL for at least 6 months prior to surgery, N=5) who underwent elective orchiectomy for gender reassignment surgery at the Metropolitan Centre of Plastic Surgery in Montreal. We selected four ATP-binding cassette (ABC) transporters, six solute-carrier (SLC) transporters and two cytochrome P450 (CYP450) drug metabolic enzymes to study based on their relevance to ARV disposition, and assessed their gene and protein expression as well as tissue localization.

Results: In testicular tissues, we found that MRP2 and OATP2B1 were highly expressed at the mRNA level, BCRP showed moderate expression, while expression of P-gp, MRP1, OATP1A2, OATP1B1, OAT1, OCT1, CNT1, ENT2, CYP2D6 and CYP3A4 were low. However, we were able to detect robust protein expression for all transporters and metabolic enzymes analysed with the exception of OATP1A2 and OCT1. Overall, gene and protein expression did not differ significantly between the uninfected and ART-treated HIV-1-infected men. Our fluorescence microscopy results also indicate that transporters and metabolic enzymes are not limited to BTB localization but can be found throughout the testicular tissue.

Conclusions: It has been well documented that drug transporters and metabolic enzymes are capable of interacting with many commonly used ARVs, and could significantly affect drug disposition into tissues, especially at key blood-tissue barriers such as the blood-brain barrier. Our data are the first to demonstrate protein expression and localization of key drug transporters and metabolic enzymes in the testes of ART-treated HIV-1 infected men. Their presence suggests the testes are a complex pharmacological compartment that could limit the penetration of several ARVs in this tissue. *(Supported by CIHR and OGS)*

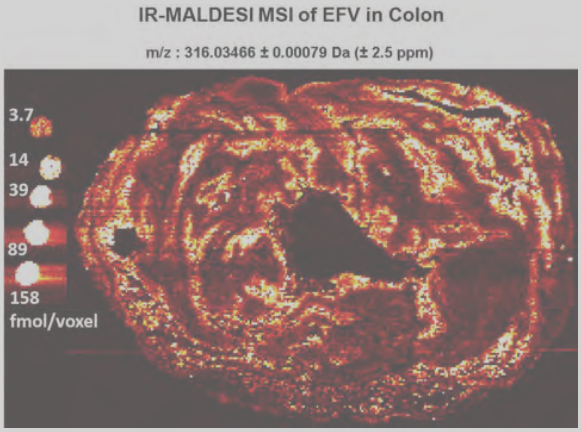
535 Imaging the Spatial Distribution of Efavirenz in Intact HIV Tissue Reservoirs

Elias P. Rosen[1]; Corbin G. Thompson[2]; Mark T. Bokhart[1]; Craig Sykes[2]; Yuri Fedoriw[2]; Paul Luciw[3]; David C. Muddiman[1]; Angela D.M. Kashuba[2]
[1]North Carolina State University, Raleigh, NC, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]University of California Davis, Davis, CA, US

Background: Methods to accurately evaluate ARV biodistribution within tissues are needed to design effective HIV therapy and eradication strategies. Here, we characterize the spatial distribution of efavirenz (EFV) within suspected reservoir tissues of a primate model using a novel approach to mass spectrometry imaging (MSI).

Methods: Reservoir tissues (GALT, lymph nodes, brain, testes) were removed at necropsy from an uninfected rhesus macaque dosed orally to steady-state with EFV. 10 μm cryosections of snap frozen tissue were discretized into 10^{-4} mm^3 voxels, resolving 100 μm features, and analyzed using an infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) source coupled to a Thermo Q-Exactive mass spectrometer. Response was calibrated by EFV standards on blank tissue, with a limit of detection of 180 attomole/voxel (57 fg/mm^3 tissue). The results were visualized using custom analysis software. Serial sections of tissue were utilized to validate MSI results by LC-MS, and stained to correlate observed EFV response with tissue morphology (H&E) and immunohistochemistry (CD3 staining).

Results: The presence of EFV was confirmed in all reservoir tissues by MSI, with varying total EFV penetration observed between tissue types. Mapping of EFV response indicated heterogeneous drug exposure. EFV concentration was substantially increased within the mucosa and lamina propria of the colorectal epithelium, specifically corresponding to high density of CD3+ T cells. No such mucosal enhancement was observed in the ileum. Lymph nodes showed focally increased signal in association with some, but not all, primary follicles. Within the brain, grey matter had enhanced EFV exposure relative to white matter. EFV concentration was lowest (167 pg/g tissue) in the basal ganglia, increasing to approximately two-fold in most other tissues (cerebrum, lymph nodes, spleen, testes, and most GALT), and highest in rectal tissue (3.6 fold).



Conclusions: This study is the first to map the biodistribution of an ARV in viral reservoir tissues. Differences in mucosal enhancement in the gut suggest potential differences in biologic transporter activity. Heterogeneous lymph node distribution may indicate insufficient exposure at important sites of viral replication. By differentiating and quantifying drug exposure between cell types within tissue, IR-MALDESI MSI offers a new capability to evaluate drug efficacy and will help inform the selection of optimal interventions to target active viral reservoirs.

724 Cancer in HIV-Infected Children: Record Linkage Study in South Africa

Julia Bohlius[6]; Nicky Maxwell[2]; Brian Eley[3]; Hans Prozesky[4]; Shobna Sawry[1]; Karl-Günter Technau[1]; Alan Davidson[2]; Cristina Stefan[5]; **Matthias Egger**[6]
On behalf of IeDEA Southern Africa
[1]University of the Witwatersrand, Johannesburg, South Africa; [2]University of Cape Town, Cape Town, South Africa; [3]Red Cross War Memorial Children's Hospital, Cape Town, South Africa; [4]University of Stellenbosch and Tygerberg Academic Hospital, Cape Town, South Africa; [5]Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa; [6]University of Bern, Bern, Switzerland

Background: The incidence of AIDS- and non AIDS-defining cancers in HIV-infected children and the impact of ART has not been evaluated in sub-Saharan Africa. We examined the incidence of cancer in HIV-infected children enrolled in antiretroviral therapy (ART) programmes in South Africa, using record linkage techniques.

Methods: We linked records of patients aged ≤16 years from five ART programmes (Harriet Shezi and Rahima Moosa in Johannesburg; Khayelitsha, Red Cross and Tygerberg in Cape Town) to the records of the four corresponding paediatric oncology units (Baragwanath and Charlotte Maxeke in Johannesburg; Red Cross and Tygerberg in Cape Town). Records were linked based on folder numbers, names, birth date and sex. Missing CD4 cell counts and percentages were multiply imputed. We calculated incidence rates and hazard ratios (HR) from Cox regression models including ART, sex, age, and immunodeficiency.

Results: Data of 11,707 HIV-infected children (29,348 person-years [pys]) were included in the analysis. Median age at enrolment was 6 years in children developing and 2.5 years in children not developing cancer. We identified 24 incident cancer cases, for an incidence rate of 82/100,000 pys (95% CI 55-122). Kaposi Sarcoma and Non Hodgkin Lymphoma were the most frequent cancers with incidence rates of 34 and 31/100,000 pys, respectively. There were few non AIDS-defining malignancies. In multivariate analysis, children on ART had a lower risk of developing cancer compared to children not on ART. The risk of developing cancer increased with age and more advanced immunodeficiency (Table). In children with cancer, one year survival was 73% (95% CI 61-82%).

Risk of developing cancer among HIV-infected children in South Africa

		Univariable analyses	Multivariable analyses
		HR (95% CI)	HR (95% CI)
ART	Not on ART	1	1
	On ART	0.43 (0.15-1.22)	0.28 (0.09-0.85)
Gender	Male	1	1
	Female	0.74 (0.33-1.67)	0.71 (0.31-1.61)
Age	< 3 years	1	1
	3 to 5	2.99 (0.66 - 13.61)	2.91 (0.64 - 13.25)
	5 to 10	5.38 (1.64 - 17.65)	5.59 (1.71 - 18.35)
	> 10 years	8.30 (2.21 - 31.22)	8.69 (2.30 - 32.80)
Immunodeficiency	None/mild	1	1
	Advanced/severe	1.87 (0.40 - 8.72)	3.69 (1.11 - 12.29)

HR: hazard ratio, ART: antiretroviral therapy; CI: confidence interval

Conclusions: ART reduces the risk of developing cancer in HIV-infected children in South Africa. Early linkage to care and early start of ART may help to further reduce the burden of cancer in these children.

725 High Cancer Risk Among the HIV-Infected Elderly in the United States

Elizabeth L. Yanik; Hormuzd A. Katki; Eric A. Engels
National Cancer Institute (NCI), Rockville, MD, US

Background: HIV-infected people have higher risk of many cancers compared to HIV-uninfected people, but it is unclear if the magnitude of this elevated risk is consistent across age groups. As the proportion of HIV-infected people over age 65 is increasing over time and the elderly population is known to have high cancer risk, it is important to understand the relationship between HIV and cancer in this age group.

Methods: We conducted a case-cohort study that included a 5% sample of Medicare enrollees and all cancer cases ≥65 years of age identified through the Surveillance, Epidemiology, and End Results cancer registries. Non-melanoma skin cancers were not captured. HIV infection was defined through Medicare diagnosis claims. Weighted Cox regression was used to estimate associations between HIV and cancer incidence adjusting for age, race, sex, and calendar year. The absolute risk of cancer over time was calculated accounting for the competing risk of death.

Results: Among 469,954 people in the 5% Medicare sample, 0.08% had an HIV diagnosis. In total, 835,450 cancer cases were identified in cancer registries. Among HIV-infected people, lung and prostate cancers were most common (N=111 each), followed by non-Hodgkin lymphoma (NHL) (N=57). HIV was strongly associated with incidence of Kaposi sarcoma, anal cancer and Hodgkin lymphoma (hazard ratios of 104, 30, and 12, respectively, Table 1). HIV was also associated with incidence of liver cancer, NHL, and lung cancer, but elevations in risk were lower (hazard ratios of 5, 3 and 2, respectively). Among NHL subtypes, HIV was associated with diffuse large B-cell lymphoma and Burkitt lymphoma, but no association was found with other specified NHL subtypes (which comprised 60% of cases in uninfected people). HIV was associated with lower prostate cancer incidence. Over a 1-year period, 2.5% of the HIV-infected elderly were diagnosed with cancer; by 5 years, this proportion increased to 10.2%.

Table 1: Cancer incidence among HIV-infected and HIV-uninfected individuals over the age of 65

	Incidence Rate*(N)		Hazard Ratio (95%CI)	
Cancer Type	HIV+	HIV-	Unadjusted	Adjusted†
Kaposi sarcoma	63.5 (12)	0.9 (398)	68.81 (38.14-124.15)	104.49 (56.66-192.69)
Non-Hodgkin lymphoma	304.0 (57)	113.2 (49,918)	2.63 (1.97-3.51)	3.48 (2.59-4.67)
Diffuse large B-cell lymphoma	139.0 (26)	30.1 (13,235)	4.53 (3.02-6.80)	6.24 (4.14-9.41)
Burkitt lymphoma	16.1 (3)	0.7 (304)	22.73 (7.24-71.37)	25.15 (7.99-79.14)
Other Specified	75.0 (14)	68.3 (30,071)	1.07 (0.62-1.83)	1.36 (0.79-2.34)
Unspecified	75.0 (14)	14.4 (6,308)	5.10 (2.97-8.76)	7.61 (4.41-13.12)
Hodgkin lymphoma	42.3 (8)	4.0 (1,752)	10.50 (5.18-21.29)	11.50 (5.65-23.42)
Anus	141.9 (27)	5.0 (2,212)	27.68 (18.56-41.27)	29.96 (19.98-44.92)
Liver	116.5 (22)	22.2 (9,806)	5.15 (3.33-7.98)	4.86 (3.12-7.56)
Lung	582.0 (111)	336.6 (148,217)	1.69 (1.35-2.12)	1.78 (1.42-2.23)
Colorectum	212.6 (40)	230.0 (101,085)	0.91 (0.65-1.27)	1.08 (0.77-1.51)
Breast‡	325.5 (16)	362.1 (94,257)	0.88 (0.51-1.52)	0.96 (0.56-1.65)
Prostate‡	805.1 (111)	854.2 (148,504)	0.92 (0.73-1.17)	0.78 (0.61-0.99)

*Incidence is per 100,000 person-years.

†Hazard ratios are adjusted for sex, race, age at start of follow-up, and calendar year at start of follow-up.

‡Breast cancer incidence was only assessed among women. Prostate cancer incidence was only assessed among men.

Conclusions: HIV infection in the elderly is associated with higher risk for many cancers identified as HIV-associated in younger populations. The relative elevation in NHL incidence is notably lower, but this reflects the high frequency in elderly adults of NHL subtypes less strongly associated with HIV. Given the increased risk associated with both aging and HIV, the elderly HIV-infected population has a sizeable absolute risk of cancer, highlighting the need for cancer prevention and screening efforts in this group.

726 Smoking Outweighs HIV-Related Risk Factors for Non–AIDS-Defining Cancers

Keri N. Althoff[1]; Stephen J. Gange[1]; Chad Achenbach[2]; Lisa P. Jacobson[1]; Angel M. Mayor[3]; Michael J. Silverberg[4]; Amy Justice[5]; Richard Moore[6]; Yuezhou Jing[1]; Kelly Gebo[6]
On behalf of the North American AIDS Cohort Collaboration on Research and Design

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [3]Universidad Central del Caribe, Bayamon, US; [4]Kaiser Permanente Northern California, Oakland, CA, US; [5]Veterans Affairs Connecticut Healthcare System and Yale Schools of Medicine and Public Health, New Haven, CT, US; [6]Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: The increased burden of non-AIDS-defining cancer (NADC) in HIV-infected adults is likely driven by both HIV-related and other cancer risk factors. The objective of this study is to estimate the population attributable fraction (PAF) for smoking and HIV-related risk factors for NADC, interpreted as the proportion of NADC that could be avoided in HIV-infected adults if all participants had the reference group exposure level.

Methods: Adults (≥18 years) participating in one of 16 contributing cohorts to the North American AIDS Cohort Collaboration on Research and Design who were observed for validated NADC diagnosis from January 1, 2000 to December 31, 2009 were included in this analysis. HIV-related risk factors included CD4 count <200 cells/mm^3, HIV RNA ≥200 copies/mL, and clinical AIDS diagnosis. Hepatitis B (HBV) and C (HCV) infections and smoking were also examined. Data on alcohol use, BMI, and HPV infections were not currently available. Risk factors were measured at study entry, with the exception of time-dependent CD4 count and HIV RNA. Cox proportional hazard models with piecewise constant baseline hazard functions were used to estimate adjusted hazard ratios (aHR) and 95% confidence intervals ([,]). The PAFs for the modifiable risk factors of interest were estimated using the methodology described by Laaksonen, *et al*.

Results: Among 39,554 adults who contributed 159,914 person-years, there were 592 incident cancer outcomes distributed as 101 (17%) lung, 96 (16%) anal, 60 (10%) prostate, 54 (9%) Hodgkin, 42 (7%) liver, and 42 (7%) breast cancers. No other cancer type represented more than 5% of the NADC. At baseline, participants who developed NADC were older and had greater proportions with a history of smoking, dyslipidemia, HBV, HCV, and an AIDS diagnosis compared to those without NADC. The PAFs for the variables in the final model can be seen in Figure 1. After excluding lung cancers from the analysis, the PAF for smoking was 39% [23%, 52%].

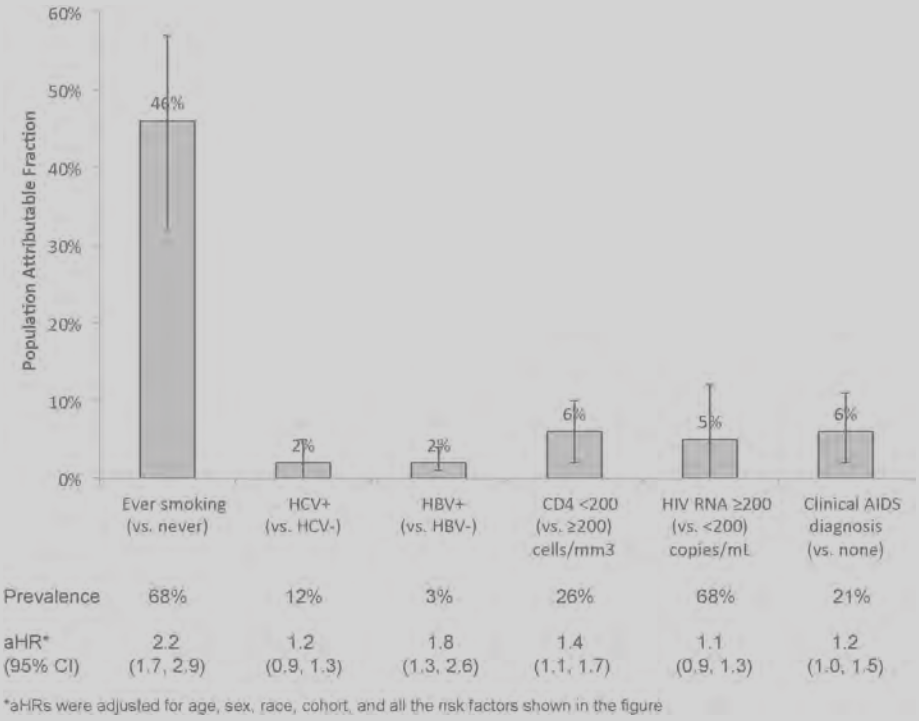


Figure 1: Population attributable fractions and 95% confidence intervals for smoking and HIV-related risk factors for non-AIDS-defining cancers

Conclusions: Programs to prevent smoking initiation among adolescents and young adults at-risk for HIV could prevent up to 46% of NADC in HIV-infected adults. Using ART to preserve immune status, maintain HIV viral suppression, and prevent AIDS-defining illnesses could prevent up to 6% of NADC in HIV-infected adults. In order to reduce the NADC burden in HIV-infected adults, effective interventions to reduce smoking are needed with a continued focus on HIV treatment.

727 High Frequency of Early Lung Cancer Diagnosis With Chest CT in HIV-Infected Smokers

Alain Makinson[1]; Sabrina Eymard-Duvernay[2]; François Raffi[3]; Fabrice Bonnet[4]; Laurence Thirard[5]; Pierre Tattevin[6]; Sophie Abgrall[7]; Jacques Reynes[1]; Vincent Le Moing[1]
on behalf of the ANRS EP48 HIV CHEST Study Team

[1]University Hospital Montpellier, UMI233, Montpellier, France; [2]UMI 233, IRD, University Montpellier 1, Montpellier, France; [3]Nantes University Hospital, Nantes, France; [4]University Hospital Bordeaux, Inserm U897, Bordeaux, France; [5]Tourcoing University Hospital, Tourcoing, France; [6]Pontchaillou University Hospital, Rennes, France; [7]University Hospital Avicennes, Bobigny, France; [8]ANRS, Paris, France

Background: The National Lung Screening Trial has provided compelling evidence of the efficacy of lung cancer screening using chest low-dose computed tomography (LDCT) to reduce lung cancer mortality, but further studies are needed to evaluate LDCT screening in different populations. We sought to study the feasibility and to identify specificities of early lung cancer diagnosis with LDCT in HIV-infected smokers.

Methods: The ANRS EP48 HIV CHEST study is a French, multicentre, prospective study consisting of a one round, millimetric, chest LDCT of HIV-infected subjects ≥ 40 years with a history of cumulative smoking within the last 3 years ≥ 20 pack-years, a CD4 T-lymphocyte nadir cell count < 350/µl, and a last CD4-T cell count > 100 cells/µl. A significant nodule on baseline CT, inducing CT follow up or immediate diagnostic procedures, was defined by a solid or partly solid nodule ≥ 5 mm or a non solid nodule ≥ 8 mm. Follow up and biopsy procedures were suggested in a workup algorithm, with a systematic follow-up of 2 years. Under the hypothesis of a 2.6 increased risk of lung cancer in HIV-infected smokers versus HIV-uninfected counterparts, we estimated lung cancer prevalence to be 3%. Hence, we aimed to enrol 445 patients, and expected 13 diagnosis of lung cancer [95% Confidence Interval, 7-22].

Results: Between March 2011 and June 2012, 442 subjects were enrolled. Median age was 49.8 years, (interquartile range (IQR) 46.3-53.9), 84% were men, median cumulative smoking was 30 pack-years (IQR 25-40), median last CD4 and nadir CD4 cell counts were 574/µl (IQR 408-765) and 168/µl (IQR 75-256) respectively, and 90% had a plasma HIV RNA < 50 copies/ml. A significant nodule was reported in 94 (21%) subjects on baseline CT. Lung cancer (5 staged IA) was diagnosed in 8 subjects (1.81 %), all but one in subjects aged < 55 years (table). There were no serious adverse events due to diagnostic procedures, and 29 subjects were lost to follow up.

Age (yr)	Sex	Lung cancer type	Stage	Smoking (pack-years)	Nadir CD4 count (cells/µl)	Last CD4 value (cells/µl)	Time (wks) between baseline CT and lung cancer diagnosis
45	M	Adenocarcinoma	IA	30	160	637	23
46	F	Adenocarcinoma	IV	52	132	597	76
49	M	Adenocarcinoma	IA	45	321	378	70
50	F	Adenocarcinoma	IV	27	60	590	12
52	M	Adenocarcinoma	IV	35	236	568	66
52	M	Adenocarcinoma	IA	60	214	859	7
54	M	Squamous cell	IA	28	71	345	23
56	M	Adenocarcinoma	IA	34	201	480	7

M : Male; F: Female

Conclusions: Early lung cancer diagnosis and nodule follow up with LDCT are feasible in HIV-infected smokers. Prevalence of lung cancer was within expected range and 5/8 cancers were surgically curable stage IA. The rate of significant nodules on baseline CT was not higher than the ranges published in non HIV-infected screening studies. Lung cancer

screening of subjects between the ages of 55-74 years as recommended in the general population may miss substantial numbers of cancers in HIV-infected smokers with a nadir CD4 cell count < 350/μl.

728 CD4 Measures as Predictors of Lung Cancer Risk and Prognosis in HIV Infection

Keith Sigel[1]; Kristina Crothers[2]; Kirsha Gordon[3]; Sheldon Brown[4]; David Rimland[5]; Maria Rodriguez-Barradas[6]; Cynthia Gibert[7]; Matthew B. Goetz[8]; Roger Bedimo[9]; Robert Dubrow[10]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, US; [2]University of Washington School of Medicine, Seattle, WA, US; [3]VA Connecticut Healthcare System and Yale University Schools of Medicine and Public Health, New Haven, CT, US; [4]James J. Peters VA Medical Center, Bronx, NY, US; [5]Atlanta VA Medical Center, Atlanta, GA, US; [6]Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, US; [7]Washington DC Veterans Affairs Medical Center, Washington, DC, US; [8]Los Angeles VA Medical Center, Los Angeles, CA, US; [9]Veterans Affairs North Texas Health Care System, Dallas, TX, US; [10]Yale University School of Public Health, New Haven, CT, US

Background: Immunodeficiency may adversely affect both lung cancer risk and outcomes in the setting of HIV infection. Using data from a large HIV cohort, we investigated relationships between 1) recent and cumulative measures of CD4 and CD8 count and lung cancer incidence and 2) CD4 measures and lung cancer prognosis.

Methods: We followed 26,065 HIV+ subjects from the Veterans Aging Cohort Study (VACS) for a minimum of 2 years, during 1999-2010. We linked VACS with the VA Central Cancer Registry to obtain incident, pathologically confirmed lung cancer cases. Our exposures of interest were longitudinal CD4 (<200 cells/mm^3 [c/mm^3], 200-500 c/mm^3 or >500 c/mm^3), CD4/CD8 (<0.4 or ≥0.4) and CD8 (≥850 c/mm^3 or <850 c/mm^3). We used Cox regression models to investigate the effect of time-updated CD4, CD4/CD8 ratio and CD8 measures on lung cancer risk, including values lagged 12 months, and 12- and 24-month simple moving averages. Models were adjusted for age, sex, race/ethnicity, smoking, and history of pneumonia and COPD. We then collected all non-small cell lung cancer cases from the full VACS (HIV+ and HIV- subjects from 1996-2010) and used conditional probability function regression (a competing risks method to account for higher risk of non-lung cancer death in HIV+) to compare lung cancer-specific survival in 3 groups: HIV- (n=679), HIV+ with CD4≥200 c/mm^3 at cancer diagnosis (n=299) and HIV+ with CD4<200 c/mm3 at cancer diagnosis (n=113). These analyses were adjusted for demographics, comorbidity score, cancer stage and histology, cancer diagnosis year, and cancer treatment.

Results: We identified 325 (1.2%) cases of incident lung cancer in our cohort. In adjusted models (Table 1), a 12 month lagged CD4 count <200 c/mm^3 as well as moving averages of both CD4<200 c/mm^3 and CD4 200-500 c/mm^3 were significantly associated with increased lung cancer incidence. In similar adjusted models, 12-month moving averages of CD4/CD8 ratio <0.4 were also significantly associated with increased risk of lung cancer. Among lung cancer cases, lung cancer-specific survival did not differ between either of the HIV+ groups and the HIV- group (p>0.05) after adjustment.

Table 1. Adjusted hazard ratios for lung cancer by CD4, CD4/CD8 ratio, and CD8 exposures.

Analyses	Lung Cancer Incidence	
	Hazard Ratio*	95% CI
CD4 Analyses		
12 Month Lagged Value		
<200 cells/mm^3	1.6	1.2-2.2
200-500 cells/mm^3	1.2	0.9-1.5
>500 cells/mm^3	Ref	Ref
12-Month Moving Average		
<200 cells/mm^3	2.0	1.4-2.7
200-500 cells/mm^3	1.4	1.1-1.8
>500 cells/mm^3	Ref	Ref
24-Month Moving Average		
<200 cells/mm^3	1.7	1.2-2.4
200-500 cells/mm^3	1.3	1.1-1.7
>500 cells/mm^3	Ref	Ref
CD4/CD8 Ratio Analyses		
12 Month Lagged Value		
<0.4	1.3	0.99-1.7
≥0.4	Ref	Ref
12-Month Moving Average		
<0.4	1.7	1.3-2.1
≥0.4	Ref	Ref
24-Month Moving Average		
<0.4	1.2	0.9-1.5
≥0.4	Ref	Ref
CD8 Analyses		
12 Month Lagged Value		
<850 cells/mm^3	0.9	0.7-1.2
≥850 cells/mm^3	Ref	Ref
12-Month Moving Average		
<850 cells/mm^3	1.0	0.8-1.3
≥850 cells/mm^3	Ref	Ref
24-Month Moving Average		
<850 cells/mm^3	1.0	0.8-1.3
≥850 cells/mm^3	Ref	Ref

*Individual time-updated Cox regression models for risk of lung cancer adjusted for age, sex, race/ethnicity, smoking status, history of pneumonia, and history of COPD

Table 1. Adjusted hazard ratios for lung cancer by CD4, CD4/CD8 ratio, and CD8 exposures.

Conclusions: In our large HIV cohort, we found that several measures of recent and cumulative exposure to immunodeficiency were associated with increased lung cancer risk. CD4 count at time of cancer diagnosis was not associated with cancer-specific survival after accounting for competing risk of non-lung cancer death.

834 Local and Systemic Humoral Responses to Cryptococcal Meningitis in Patients With AIDS

Erin E. Finn[1]; Jordan Janoff[1]; Jeremy Rahkola[1]; David B. Meya[2]; Samuel Okurut[2]; Andrew D. Kambugu[2]; Paul Bohjanen[3]; Kirsten Nielsen[3]; David R. Boulware[3]; Edward N. Janoff[1]

[1]Mucosal and Vaccine Research Colorado, Aurora, CO, US; [2]Makerere University College of Health Sciences, Kampala, Uganda; [3]University of Minnesota, Minneapolis, MN, US

Background: Antibodies may support protection against meningitis caused by *Cryptococcus neoformans* (CM), a prominent cause of disease and death in persons with AIDS, among whom antibody defects are common.

Methods: We measured total and Cryptococcus-specific IgG and IgM antibody levels by ELISA in serum and cerebrospinal fluid (CSF) from 41 antiretroviral therapy naïve adults with AIDS at the time of CM diagnosis in Kampala, Uganda. Cryptococcus-specific antibodies were directed against capsular glucuronoxylomannan (GXM) or unencapsulated organisms. Immune complexes (IC) were dissociated and neutralized with acid treatment and glycine.

Results: The median CD4+ T cell count was 16/μL and log_{10} HIV RNA was 5.33 copies/mL. CSF-analysis showed median protein of 70 mg/dL, WBC of 30/mL [43% had <5 cells], cryptococcal antigen (CrAg) titer of 1:4,000 and cryptococcal colony forming units of log_{10} 5.4/mL. Total IgG in CSF exceeded IgM by over 20 fold (median 127 vs. 5.8 μg/mL). Levels of IgG and IgM specific to GXM were greater than levels specific to unencapsulated organisms. We detected GXM-specific IgG and IgM in CSF of 46% and 24% of subjects, respectively, and in 100% of sera. The antibodies detected in CSF were specific for GXM based on cross-adsorption with heterologous polysaccharides and proteins, but the specificity of IgM exceeded that of IgG. In the CSF, GXM-IgM was produced locally, whereas the GXM-IgG was likely transferred from serum based on the ratios of GXM-specific to total IgM and IgG in CSF and serum. The majority of GXM-IgG but not IgM in the CSF was bound by local capsular GXM as levels increased by 10-fold upon dissociation of IC. IC-bound antibodies had greater avidity than antibodies freely circulating in CSF. Levels of GXM-IgG or -IgM did not correlate with CSF WBC, protein, CrAg titer or mortality (11 of 41 died [26.8%] within 30 days).

Conclusions: Specific antibodies that recognize the predominant capsular polysaccharide of *C. neoformans* (GXM) are present in the CSF of a subset of AIDS patients with CM. GXM-IgM, although present in fewer patients, was higher in concentration, specificity and avidity than GXM-IgG and was more likely produced locally at the site of infection. Enhancing levels of such antibodies may support opsonization of *C. neoformans*, promote cytokine production and cellular immune responses to the organism, and thereby faciliate protection against these common and often fatal infections.

835 Antiretroviral Therapy Alters the CSF Immune Response in Cryptococcal Meningitis

James E. Scriven[1]; Britta Urban[1]; Lisa Graham[2]; Charlotte Schutz[2]; Robert J. Wilkinson[3]; David R. Boulware[4]; David Lalloo[1]; Graeme Meintjes[2]

[1]Liverpool School of Tropical Medicine, Liverpool, United Kingdom; [2]University of Cape Town, Cape Town, South Africa; [3]Imperial College London, London, United Kingdom; [4]University of Minnesota, Minneapolis, MN, US

Background: Cryptococcal meningitis (CM) is an important opportunistic infection in sub-Saharan Africa. Animal models suggest a M2 (alternatively activated) macrophage phenotype and Th2 response are detrimental during infection but studies in humans are limited. To address this we characterized the CSF immune response in HIV-associated CM, examined the effects of ART, and explored the relationship between CSF immune response, fungal burden and mortality.

Methods: A prospective cohort study was conducted in South Africa. Persons with CM were enrolled and followed for 12 weeks. CSF immune response was examined using 11-colour flow cytometry and 17-plex luminex analysis. Fungal burden was measured using quantitative culture. Data were analysed using principal component analysis; p<0.05 with a false discovery rate (q) <0.1 were used to infer statistical significance.

Results: 57 subjects were enrolled: 42 not taking ART, 8 on effective ART and 7 with virological failure on ART. Median CD4 count was 34 cells/μL and median CSF WCC 18/μL. CD8 T cells were the most frequent CSF cell followed by neutrophils, macrophages and CD4 T cells (median 50%, 12%, 6.7% and 6.2% WCC respectively). Compared to individuals not on ART, the CSF of those taking effective ART had significantly increased CD4 T cells, decreased CD8 T cells, increased CD4/CD8 ratio and increased CD206 expression on CD14+ and CD14- macrophages - suggesting M2 phenotype (**table 1**). CD206 expression was inversely correlated with plasma viral load (even in persons not taking ART (r=-0.59, p=0.0001)) but was not associated with fungal burden (r=-0.02, p=0.893). Fungal burden was inversely correlated with CSF GCSF, IL6, CD4, CD8, CD4-CD8- and NK cells (r= -.49, -.41 -.61, -.55, -.49, -.40 respectively; all p <.05 and q<.1). Non-survivors had decreased CSF CD4-CD8- T cells and reduced CSF IFNγ but this was not significant when adjusted for multiple comparisons (p=.021 q=.92; p=.038, q=.97; respectively).

CSF Parameter	Effective ART		No ART		p	q
	Mean (geo)	95% CI	Mean (geo)	95% CI		
CD4 (%WCC)	13.7	7.7-24.8	4.5	3.4-6.1	0.0026	0.040
CD8 (% WCC)	19.1	11.1-32.8	47.5	40.5-55.7	0.0000	0.002
Large T cells (%WCC)	0.10	0.03-0.3	1.05	0.73-1.52	0.0000	0.023
CD4/CD8 ratio	0.72	0.29-1.75	0.08	0.05-0.13	0.0006	0.001
HLA-DR+ (% CSF CD4)	29	19-46	45	40-50	0.0075	0.060
CD206 CD14+M (MFI)	6568	3229-13227	2752	2143-3498	0.0055	0.050
CD206 CD14-M (MFI)	3327	1003-11038	938	702-1253	0.0019	0.023
CD16 CD14-M (MFI)	413	299-571	238	197-286	0.0120	0.073

Table 1. *Immune parameters that differed significantly between subjects taking effective ART and those who were not. Geometric means are displayed; parametric tests were performed on log2 transformed variables. Q values refer to the false discovery rate. "Large T cells" were a secondary population of T cells with increased forward scatter. WCC=white cell count; M=macrophage*

Conclusions: In CM, ART is associated with an increased CSF CD4/CD8 ratio and an increased M2 macrophage phenotype, likely mediated through effects on HIV viral load. In contrast to animal data the M2 phenotype was not associated with increased fungal load or fatal outcome. Instead, fungal burden was negatively correlated with CSF T cells (CD8, CD4 and CD4-CD8-) and concentrations of pro-inflammatory cytokines. This is supportive of the theory that a paucity of CSF inflammation is associated with severe disease in CM.

836 Detrimental Outcomes of Unmasking Cryptococcal Meningitis With Recent ART Initiation

Joshua Rhein[1]; Katherine H. Hullsiek[1]; Nathan C. Bahr[1]; Reuben Kiggundu[3]; Darlisha Williams[3]; Henry W. Nabeta[3]; Abdu Musubire[3]; David B. Meya[3]; David R. Boulware[1]

[1]University of Minnesota, Minneapolis, MN, US; [2]University of Minnesota, Minneapolis, MN, US; [3]Makerere University College of Health Sciences, Kampala, Uganda

Background: Cryptococcal meningitis (CM) remains a major cause of HIV-related mortality in Africa. Increased antiretroviral therapy (ART) availability coupled with a lack of pre-ART cryptococcal antigen screening has led to a greater proportion of patients developing CM after initiating ART. Despite this changing epidemiology, data regarding CM in patients already receiving ART are lacking. We compared the clinical presentation and outcomes in ART-naïve and ART-experienced Ugandans.

Methods: We enrolled a prospective cohort of 165 HIV-infected persons with cryptococcosis in Kampala, Uganda from Aug 2013 to Aug 2014. Subjects were classified by ART status, the timing of ART initiation, and previous CM history. The primary endpoint was 2-week mortality. Statistical comparisons were made with Kruskal-Wallis or Fisher's Exact tests.

Results: 87% (144/165) of subjects presented with their first episode of CM whereas 13% (21/165) had a previous history of CM. Of those with first CM episode, 40% (58/144) were receiving ART at presentation, having initiated ART a median of 110 (IQR, 20-519) days prior to CM diagnosis. Those receiving ART had higher CD4 (median 32 (IQR, 10-73) vs 12 (IQR, 6-39) cells/mcL; *p*=.02) and lower CSF fungal burdens (median 4.0 (IQR, 2.5-4.9) vs 4.8 (IQR, 3.9-5.6) log_{10} CFU/mL CSF; *p*<.001). 55% (32/58) had initiated ART within the last 4 months, and 22% (13/58) initiated ART within the last 14 days. Persons starting ART <4 months prior were more likely to present with altered mental status (44% vs 19% with GCS<15, *p*=.05) despite having lower CSF fungal burdens (median 3.7 (2.3-4.3) vs 4.5 (3.4-5.1) log_{10} CFU/mL; *p*=.04) compared to those initiating ART >4 months prior to

CM diagnosis. CSF WBC did not differ. The 2-week mortality was significantly higher in those on ART for <14 days (54%) compared to those on ART for 15 days to 4 months (16%; p=.05), >4 months (12%; p=.01), or ART-naïve (24%). CM presenting after >4months on ART was an indication of virologic failure.

Conclusions: The occurrence of CM after initiating ART is now common in Africa. Although these patients have higher CD4 counts and lower fungal burdens, outcomes do not appear to be improved. Patients developing CM within 14 days of initiating ART are at a higher risk of death. Immune recovery in the setting of a CNS infection is detrimental, and management of this population requires future study. Implementing pre-ART cryptococcal antigen screening would decrease CM occurring early after ART initiation.

837 Impact of ART on Mortality in Cryptococcal Meningitis Patients: High-Income Settings

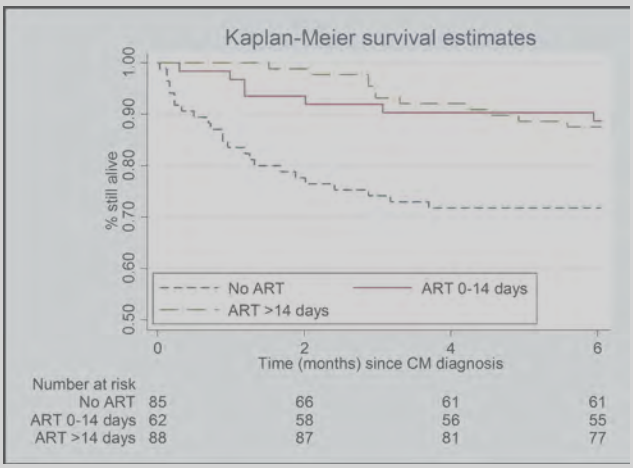
Suzanne M. Ingle[1]; Jose M. Miro[2]; Hansjakob Furrer[4]; Amy Justice[5]; Michael S. Saag[6]; Christian Manzardo[2]; Anna Esteve[7]; Lauren E. Cain[3]; Jonathan A. Sterne[1]; Margaret T. May[1]

[1]University of Bristol, Bristol, United Kingdom; [2]Hospital Clínic–L'Institut D'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain; [3]Harvard School of Public Health, Boston, MA, US; [4]Bern University Hospital and University of Bern, Bern, Switzerland; [5]Yale University School of Medicine, VA Connecticut Healthcare System, New Haven, CT, US; [6]University of Alabama at Birmingham, Birmingham, AL, US; [7]Centre d'Estudis Epidemiològics Sobre ITS/VIH/SIDA de Catalunya, Barcelona, Spain

Background: Randomised trials (RCTs) from low-income countries have shown that early ART among antiretroviral-naïve HIV-1–infected patients presenting with cryptococcal meningitis (CM) is associated with higher mortality than delayed ART. There is limited information on the impact of timing of ART on short-term mortality in patients with CM cared for in high-income settings.

Methods: Data on ART-naive patients diagnosed with CM between 1998 and 2009 were combined from cohorts contributing to the COHERE, NA-ACCORD and CNICS collaborations. Follow-up time was calculated from date of CM diagnosis to the first of death, last follow-up or 6 months post-diagnosis. We mimicked an RCT comparing regime A ("start ART within 14 days of CM diagnosis") with regime B ("defer ART until 14 -56 days after CM diagnosis"). Marginal structural models were used to compare the effects of these regimes on all-cause mortality. Models were adjusted for gender, age, mode of transmission, CD4, viral load (VL), AIDS (other than CM), year of diagnosis and whether data were European/North American.

Results: Of 235 patients (84% male) from 28 cohorts across Europe and N. America with full covariate data, 42 (18.0%) died within 6 months. Median age at CM diagnosis was 38 years (IQR 34-44). Of 150 patients (64%) who started ART, 18 (12%) died within 6 months. 7/62 (11%) patients died among those who started ART within 2 weeks of CM diagnosis, compared with 11/88 (12%) among those who started ART after 2 weeks. The graph shows crude survival over time, according to when the patient started ART. In data mimicking an RCT, there were 15 deaths (33.3 years follow-up) in regime A and 26 deaths (47.8 years) in regime B. The crude and adjusted hazard ratios comparing deferred with early treatment were 1.29 (95% CI 0.68-2.43) and 1.30 (0.66-2.55).



Kaplan-Meier survival estimates according to time of starting ART

Conclusions: We found little evidence that early ART was associated with higher mortality after CM than deferred ART, although confidence intervals were wide. Although we adjusted for potential confounding factors, confounding and selection bias may not be fully adjusted for; we aim to address this limitation by ascertaining additional information on treatment of CM after diagnosis. Mortality among patients cared for in high income settings was clearly lower than reported in the RCTs conducted in low-income countries.

838 Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis

Joshua Rhein[1]; Katherine H. Hullsiek[1]; Bozena Morawski[1]; Kyle Smith[1]; Ali Al-Hadab[1]; Abdu Musubire[2]; Darlisha Williams[2]; Kristen Nielsen[1]; David B. Meya[2]; David R. Boulware[1]

[1]University of Minnesota, Minneapolis, MN, US; [2]Makerere University College of Health Sciences, Kampala, Uganda

Background: Mortality from HIV-associated cryptococcal meningitis (CM) remains unacceptably high. Identifying new effective antifungals is of paramount importance. We evaluated the efficacy of adjunctive sertraline, previously demonstrated to be active against *Cryptococcus neoformans* both *in vitro* and in murine models.

Methods: 144 HIV-infected persons with first episode of CM were prospectively enrolled in a phase IIb, open-label clinical trial in Kampala, Uganda between Aug 2013-2014. Sertraline at doses of 100-400 mg/day was added to standard therapy (amphotericin + fluconazole 800mg/day). Early fungicidal activity (EFA) was measured as the rate of cryptococcal clearance in serial quantitative CSF cultures and calculated by mixed effect model for all participants with at least 2 CSF cultures (N=122). Sertraline concentrations in plasma were measured using high performance chromatography–mass spectrometry in 77 subjects to evaluate how rapidly sertraline achieves steady state. *In vitro* susceptibility was assessed on a subset of *C. neoformans* isolates (N=95) to determine target 90% minimum inhibitory concentration (MIC90).

Results: Those receiving any dose of sertraline had 28% faster rate of clearance compared with recent historical controls (Table): EFA -0.39 vs. -0.30 for those with vs. without sertraline (p=0.03). Sertraline reached steady state in plasma by day 7, with a median level of 215 (IQR, 126-305) ng/mL at 200mg/day and 400 (IQR, 281-556) ng/mL at 400mg/day. Plasma levels were 68% of steady state levels by day 3. The projected steady state brain tissue concentration at 200mg/day was a median of 3.5 (IQR, 2.1-5.0) mcg/mL and at 400mg/day was 6.6 (4.6-9.2) mcg/mL. Among *Cryptococcus* isolates, the MIC90 was ≤1 mcg/mL for 9.5%, ≤2 mcg/mL for 30.5%, ≤4 mcg/mL for 84%, and ≤8 mcg/mL for 99% of isolates. *In vitro* synergy studies (n=9) found a median 2-fold reduction in the MIC90 with a combination of sertraline and fluconazole. For sertraline at doses 200-400mg/day, the incidence of paradoxical IRIS or relapse through 12 weeks was 1%.

Table: Early Fungicidal Activity of the Rate of CSF Clearance in Cryptococcal Meningitis

Anti-Fungal Induction Regimen	N	EFA[1] (95% CI) log_{10} CFU/mL
Standard therapy [2] + 100 mg/day sertraline	13	-0.37 (-0.41, -0.24)
Standard therapy [2] + 200 mg/day sertraline	40	-0.40 (-0.48, -0.31)
Standard therapy [2] + 300 mg/day sertraline	38	-0.39 (-0.47, -0.32)
Standard therapy [2] + 400 mg/day sertraline	31	-0.37 (-0.47, -0.29)
Standard therapy + all sertraline regimens	122	-0.39 (-0.43, -0.34)
Standard therapy without sertraline [2,3]	189	-0.30 (-0.32, -0.28)

[1] EFA (Early Fungicidal Activity) estimated with longitudinal mixed models. Values are population means with 95% confidence intervals (95% CI).

[2] Standard therapy: Amphotericin B deoxycholate (0.7-1.0mg/kg/day)+ fluconazole 800mg/day.

[3] Historical controls, enrolled from November 2010 through July 2013.

Conclusions: Sertraline provides fungicidal activity against *C. neoformans* with improvements in CSF clearance rates and appears to reach therapeutic levels *in vivo*. This widely available off-patent oral medication ($0.05 per 100mg tablet) provides a promising adjunct for CM treatment when added to standard antifungal therapy. This pilot justifies a larger randomized trial to elucidate whether sertraline has a survival benefit for the treatment of CM.

1060 Trends in Sexual Behaviors Among Men Who Have Sex With Men in the United States, the Role of Antiretroviral Therapy and Seroadaptive Strategies

Gabriela Paz-Bailey[1]; Maria Mendoza[1]; Binh Le[1]; Charles E. Rose[1]; Teresa Finlayson[1]; Cyprian Wejnert[1]; Henry F. Raymond[2]; Joseph Prejean[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]San Francisco Department of Public Health, San Francisco, CA, US

Background: CDC data from the National HIV Behavioral Surveillance System (NHBS) suggest that condom use has decreased among men who have sex with men (MSM). The reasons for this decrease are not known but may reflect the adoption of risk-reduction strategies other than consistent condom use, such as engaging in unprotected sex only with partners perceived to have the same HIV status as one's own (sero-adaptive behaviors). We used data among MSM participating in NHBS to evaluate changes from 2005 to 2011 in condomless anal sex at last sex.

Methods: MSM were recruited through venue-based sampling in 2005, 2008 and 2011 in up to 21 U.S. cities. Among men reporting ≥1 male partner and self-reporting as HIV-positive or HIV-negative, we evaluated changes in condomless anal sex at last sex with a partner reported to have 1) HIV concordant status (proxy for sero-adaptive behavior), or 2) HIV-discordant or unknown status, by participant's reported HIV status and antiretroviral therapy (ART) use (HIV-positive only). We used GEE modeling with a robust variance estimation, and assumed a Poisson distribution to explore whether temporal changes in the outcomes varied by selected characteristics.

Results: In adjusted analyses among 23,125 HIV-negative MSM, concordant condomless sex at last anal sex increased significantly (20%, 22% and 24%, in 2005, 2008 and 2011, respectively, p<0.001) as well as discordant/unknown condomless sex (7%, 10%, 11%, respectively, p<0.001). Among 3,785 HIV-positive MSM, there were no significant changes in concordant (19%, 21% and 26%, p=0.14) or discordant/unknown condomless sex (14%, 16%, and 14%, p=0.11). Concordant condomless sex increased among MSM on ART (18%, 22%, and 26%, p<0.001) but not among MSM not on ART (21%, 20% and 27%, p=0.11). There were no significant changes in discordant/unknown condomless sex by ART use.

Conclusions: There were modest increases in condomless sex at last sex both with partners of concordant and discordant/unknown HIV status among HIV-negative MSM, and only with a partner of concordant status among HIV-positive MSM on ART. These data suggest that the increases in condomless sex among MSM are in part due to the adoption of sero-adaptive behaviors but that discordant condomless sex is also increasing among HIV-negative MSM. HIV-negative MSM who engage in condomless sex would benefit from having access to risk-reduction interventions, including pre-exposure prophylaxis.

1061 Changes in Condomless Sex and Serosorting Among MSM After HIV Diagnosis

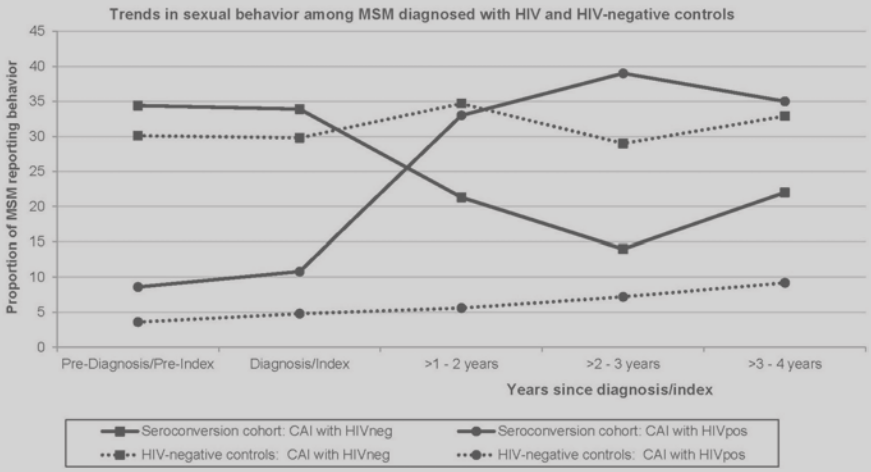
Christine M. Khosropour[2]; Julia C. Dombrowski[2]; David A. Katz[2]; Matthew R. Golden[2]

[1]University of Washington, Seattle, WA, US; [2]University of Washington, Seattle, WA, US

Background: Among men who have sex with men (MSM) diagnosed with HIV, high-risk sexual behaviors may decline in the year after diagnosis, but changes in serosorting post-diagnosis are not well defined. Few studies have assessed changes in these behaviors both pre-diagnosis and for several years after.

Methods: We created a retrospective cohort (seroconversion cohort) of MSM attending an STD clinic in Seattle, WA who tested HIV positive between 2002-2013 and had a negative HIV test ≤2 years prior to diagnosis (pre-diagnosis visit). Potential controls were MSM who never tested HIV-positive and had a negative test ≤2 years prior to a randomly selected index visit. We randomly selected 1,000 controls frequency-matched to the seroconversion cohort based on HIV diagnosis year/index date. Sexual behavior data in the 12 months prior to each visit were collected by clinicians using standardized forms or a computer self-interview as part of routine clinical care. We examined condomless anal intercourse (CAI) with HIV-negative and -positive partners at 5 time points: before diagnosis/index, at diagnosis/index, and each year up to 3 visits after diagnosis/index. We used McNemar's chi-square to compare behaviors reported at the 2 visits before/at diagnosis vs. the 3 visits after diagnosis and used linear regression to examine trends over time.

Results: There were 655 (2.5%) new HIV diagnoses at 26,144 clinic visits where MSM tested for HIV; 186 (28%) men with a new diagnosis tested negative ≤2 years before diagnosis and were included in the seroconversion cohort. The 1,000 persistently HIV-negative controls were selected from 3,083 eligible MSM. In the seroconversion cohort, the percent reporting CAI with HIV-negative partners declined after diagnosis (34% vs 19%, P=.003) while the percent reporting CAI with HIV-positive partners increased (10% vs 35%, P<.001; Figure). Thus, the proportion who serosorted (i.e. reported only HIV concordant CAI) did not change before or after diagnosis (34% vs 35%, P=.85) and remained stable in the years after diagnosis (P-value for trend post-diagnosis=.79). Among HIV-negative controls, serosorting and CAI with HIV-positive partners remained relatively constant.



Conclusions: Among MSM in our clinic, those diagnosed with HIV modified their sexual behaviors post-diagnosis based on partner HIV status and this change was sustained several years after diagnosis. These findings suggest that, among MSM, changes in sexual behavior following HIV diagnosis are large and durable.

1062 Serosorting and Sexual Risk Behavior Influenced by Perceived HIV Serostatus Among MSM

Kathleen A. Brady; Jennifer Shinefeld; Catherine Mezzacappa

Philadelphia Department of Public Health, Philadelphia, PA, US

Background: According to the CDC, unknown HIV serostatus and unprotected anal sex among men who have sex with men (MSM) contribute to high levels of new infections in this population. This study used data from the National HIV Behavioral Surveillance System (NHBS) to analyze the relationship between perceived HIV serostatus and high-risk sexual behaviors among MSM.

Methods: NHBS is conducted annually in 20 metropolitan areas using a standardized survey and free HIV testing to analyze trends in HIV risk behaviors and prevalence among high risk groups including MSM. HIV testing included a rapid test at time of interview and a confirmatory test. We combined data from the 2008 and 2011 MSM cycles in Philadelphia and performed bivariate analyses of sexual risk behaviors at last sexual encounter across perceived HIV serostatus. Perceived HIV serostatus was defined as 'known negative' for a man who had a negative HIV test in the past year, 'known positive' for a man who had ever tested positive for HIV, and 'unknown' for a man who had not had an HIV test in the past year nor previously tested positive. Serosorting is the practice of choosing a partner known to be of the same HIV serostatus in order to reduce the risk of acquiring or transmitting HIV.

Results: Of 1194 respondents, 31.3% were known negative, 5.5% known positive, and 63.2% unknown perceived serostatus. Testing revealed that 3.0% of known negative and 4.4% of unknown perceived serostatus were HIV positive. There were no differences in frequency of insertive anal sex at last encounter across perceived serostatus. Known negative men were less likely to use a condom during receptive anal intercourse (p=0.006). Approximately two-thirds of all respondents knew the HIV status of their most recent partner. Among those who knew their partner's HIV status, serosorting was extremely prevalent: 73.9% of known positive men had sex with an HIV positive partner, compared to 5.6% of unknown, and 4.4% of known negative men, (p<0.0001).

Table 1. Behaviors at last sexual encounter by perceived HIV status

	Known Negative N=373	Known Positive N=66	Unknown N=755	p-value
Actual HIV status				
Negative	97.0% (356/367)	0	95.6% (673/704)	
Positive	3.0% (11/367)	100% (66)	4.4% (31/704)	
Type of partner				
Main	34.3% (71/207)	36.1% (13/36)	37.0% (114/308)	0.37
Casual	52.2% (108/207)	41.7% (15/36)	52.0% (160/308)	
Exchange	13.5% (28/207)	22.2% (8/36)	11.0% (34/308)	
Had insertive anal sex (IAS)	61.0% (219/359)	61.5% (40/65)	59.9% (408/681)	0.92
Did not use a condom during IAS	30.1% (66/219)	37.5% (15/40)	25.5% (104/408)	0.17
Had receptive anal sex (RAS)	52.8% (189/358)	56.9% (37/65)	60.4% (411/681)	0.06
Did not use a condom during RAS	42.1% (80/190)	29.7% (11/37)	29.0% (119/411)	0.006
Relative age of partner				
Younger	31.2% (110/353)	41.5% (27/65)	34.0% (226/665)	0.30
Older	35.7% (126/353)	27.7% (18/65)	30.5% (203/665)	
Same age	33.1% (117/353)	30.8% (20/65)	35.5% (236/665)	
Knew HIV status of partner	64.1% (230/359)	70.8% (46/65)	65.5% (446/681)	0.57
Partner was HIV positive (among those who knew HIV status of partner)	4.4% (10/229)	73.9% (34/46)	5.6% (25/443)	<0.0001

Conclusions: Knowledge of HIV serostatus influences sexual behaviors among MSM, particularly through serosorting. However, over 60% of men surveyed had not been tested for HIV in the previous year and a third of men did not know the HIV status of their most recent partner. Prevention efforts should be tailored to reach those MSM who remain unaware of their HIV status.

1063 Use of the Seroadaptive Strategies of Sexual Positioning and Serosorting by MSM in Nigeria

Cristina M. Rodriguez-Hart[1]; Hongjie Liu[2]; Ifeanyi K. Orazulike[3]; Sam Zorowitz[4]; Sylvia Adebajo[5]; Lindsay Hughes[6]; Stefan Baral[7]; Merlin L. Robb[6]; William Blattner[1]; Manhattan Charurat[1]

[1]University of Maryland School of Medicine, Baltimore, MD, US; [2]University of Maryland School of Public Health, College Park, MD, US; [3]International Center on Advocacy and Rights to Health, Abuja, Nigeria; [4]Massachusetts General Hospital and Harvard Medical School, Boston, MA, US; [5]Population Council, Abuja, Nigeria; [6]US Military HIV Research Program, Bethesda, MD, US; [7]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

Background: Sexual positioning and serosorting are two seroadaptive strategies adopted by some men who have sex with men (MSM) as HIV harm reduction strategies. The current analysis investigated these factors among MSM in Nigeria, where rates of infection are 10 fold higher than in the general population, who participated in the TRUST study.

Methods: Using respondent-driven sampling, 392 eligible MSM were interviewed. A subject was considered to be engaged in sexual positioning if an HIV positive MSM who knew his status prior to the study reported only receptive anal sex for the previous 12 months or an HIV negative MSM who knew his status prior to the study reported only insertive anal sex for the previous 12 months. A subject was considered to be engaged in serosorting if he knew his HIV status prior to the study and reported having only sex partners of the same HIV status. Logistic regression with generalized estimating equations was used to analyze factors associated with engagement in positioning or serosorting.

Results: Of the 390 participants with HIV testing history and who were tested for HIV at baseline, 21% (85/390) were HIV positive and reported knowing their status, 29% (114/390) were HIV negative and reported knowing their status, 23% (89/390) were HIV positive and reported not knowing their status, and 25% (97/390) were HIV negative and reported not knowing their status.

Among HIV positive MSM who knew their HIV status, 21% (18/85) practiced receptive sex only. Among HIV negative MSM who knew their status, 39% (44/114) practiced insertive sex only. Engagement in sexual positioning was associated with older age (OR=2.15; 95%CI: 1.07-4.32), not being married to a woman (OR=2.94; 95%CI: 1.03-8.33), and communication with partners about HIV status (OR=1.84; 95%CI: 1.01-3.36). The 384 MSM who reported any sex partner data generated 1565 sex partner dyads. Serosorting took place only among 192 dyads (12%). Engagement in serosorting was associated with communication with partners about HIV status (OR=3.78; 95%CI: 2.12-6.75) and stronger friendship (OR=1.40; 95%CI: 1.11-1.76).

Table 1. Sexual positioning and serosorting by HIV testing history and HIV serostatus among men who have sex with men (MSM) in Abuja, Nigeria

	Ego Self-Reported Knowing their HIV Status Prior to the Study		Ego Self-Reported Not Knowing their HIV Status Prior to the Study	
	HIV+ Crude % (n)	HIV- Crude % (n)	HIV+ Crude % (n)	HIV- Crude % (n)
Sexual Positioning (n=number of egos)[a]	n = 85	n = 114	n = 89	n = 97
Ego's Sexual Position				
Only insertive (n=103)	15.3 (13)	38.6 (44)	16.9 (15)	32.0 (31)
Only receptive (n=81)	21.2 (18)	20.2 (23)	20.2 (18)	22.7 (22)
Dual Practice (n=201)	63.5 (54)	41.2 (47)	62.9 (56)	45.4 (44)
Serosorting (n= number of ego-alter dyads)[b]	n = 357	n = 452	n = 353	n = 403
Alter's HIV Status				
Positive (n=58)	12.6 (45)	1.3 (6)	1.1 (4)	.7 (3)
Negative (n=415)	19.0 (68)	32.5 (147)	26.3 (93)	26.6 (107)
Unknown (n=1092)	68.3 (244)	66.2 (299)	72.5 (256)	72.7 (293)

[a] 7 egos were excluded from the analysis of sexual positioning. Of the 7, sexual positioning could not be calculated for 5 egos and 2 egos reported being HIV+ and knowing this status before the study but tested negative for HIV at study baseline.
[b] 8 egos were excluded from the analysis of serosorting. Of the 8, 6 did not report information on any alters in their sexual network and 2 egos reported being HIV+ and knowing this status before the study but tested negative for HIV at study baseline.

Conclusions: With this low level of engagement in harm reduction strategies among Nigerian MSM, interventions that promote communication between sex partners to adopt harm reduction and engage the full spectrum of combination prevention strategies promoted by the TRUST intervention are a focus of ongoing study, including how to influence normative behaviors in sexual networks.

1104 The Lifetime Medical Cost Savings From Preventing HIV in the United States

Bruce R. Schackman[1]; John Fleishman[6]; Amanda Su[2]; Richard Moore[5]; Rochelle Walensky[2]; David Paltiel[3]; Milton Weinstein[4]; Kenneth Freedberg[2]; Kelly Gebo[5]; Elena Losina[2]

[1]Weill Cornell Medical College, New York, NY, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Yale School of Public Health, New Haven, CT, US; [4]Harvard School of Public Health, Boston, MA, US; [5]Johns Hopkins University School of Medicine, Baltimore, MD, US; [6]Agency for Healthcare Research and Quality, Rockville, MD, US

Background: Enhanced HIV prevention interventions, such as pre-exposure prophylaxis for high-risk individuals, require substantial investments. We sought to estimate the medical cost saved by averting one HIV infection in the United States.

Methods: We estimated lifetime medical costs in persons with and without HIV to determine the cost saved by preventing one HIV infection. We used a computer simulation model of HIV disease and treatment (CEPAC) to project CD4 cell count, antiretroviral treatment status, and mortality after HIV infection. Annual medical cost estimates for HIV-infected persons, adjusted for age, sex, race/ethnicity, and transmission risk group, were from the HIV Research Network (range $1,854-$4,545/month) and for HIV-uninfected persons were from the Medical Expenditure Panel Survey (range $73-$628/month). Results are reported as lifetime medical costs from the US health system perspective discounted at 3% (2012 US dollars).

Results: The estimated discounted lifetime cost for persons who become HIV infected at age 35 is $326,500 (60% for antiretroviral medications, 15% for other medications, 25% for non-drug costs). For individuals who remain uninfected, but at high risk for infection, the discounted lifetime cost estimate is $96,700. The medical cost saved by avoiding one HIV infection is $229,800. The cost saved would reach $338,400 if all HIV-infected individuals presented early and remained in care. Cost savings are higher taking into account secondary infections avoided and lower if HIV infections are temporarily delayed rather than permanently avoided.

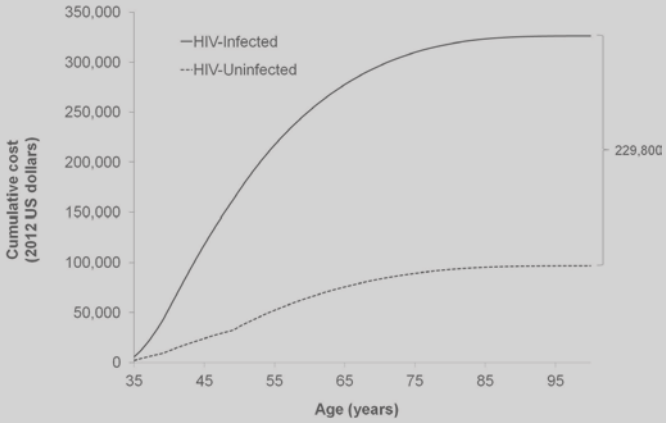


Figure 1: Cumulative discounted lifetime costs from time of infection at age 35 (2012 US dollars)

Conclusions: The potential medical cost savings from HIV prevention in the US are substantial given the high cost of HIV disease treatment.

1119 Survival Benefits Attributable to the Brazilian National ART Policy

Paula M. Luz[1]; Michael P. Girouard[2]; Beatriz Grinsztejn[1]; Kenneth Freedberg[2]; Valdilea Veloso[1]; Elena Losina[4]; Claudio Struchiner[1]; Robert Parker[2]; David Paltiel[3]; Rochelle Walensky[2]

[1]Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil; [2]Massachusetts General Hospital, Boston, MA, US; [3]Yale School of Public Health, New Haven, CT, US; [4]Brigham and Women's Hospital, Boston, MA, US

Background: In Brazil, universal provision of antiretroviral therapy (ART) has been guaranteed free of charge to patients since 1996. We sought to quantify the survival benefits attributable to this policy.

Methods: We used a mathematical model of HIV disease (CEPAC-International) to estimate life expectancy of HIV-infected patients initiating ART between 1997 and 2013 in Brazil. We divided this timeframe into 5 eras, reflecting improvements in virologic and immunologic response to ART and in regimen sequencing over time. Input parameters were from the HIV Clinical Cohort at the Evandro Chagas Clinical Research Institute (Oswaldo Cruz Foundation) and from published Brazilian governmental data. Era-specific mean CD4 count at ART initiation ranged from 134/μL (Era 1) to 384/μL (Era 5). We included a loss to follow-up rate in each cohort of 10.1/1000 person-years. The 2014-censored and lifetime survival benefit attributable to each era were calculated as the sum of patients initiating ART in each cohort of a given era multiplied by the per-person survival increase attributable to ART in that era compared to pre-ART prophylaxis alone.

Results: In total, 556,829 individuals were estimated to have initiated ART in Brazil between 1997 and 2013 (Figure 1). Patients initiating ART in Era 1 had an estimated 2014-censored per-person life expectancy of 6.3 years compared to 2.9 years for pre-ART prophylaxis. Assuming no further improvements in care over time, projected lifetime per-person life expectancy increased from pre-ART (2.9 years) to 11.4, 17.0, 20.6, 23.7, and 25.7 years in Eras 1, 2, 3, 4, and 5, respectively. Total estimated population lifetime survival benefit for all persons starting ART from 1997 to 2013 in Brazil was 9.2 million life-years, with 1.3 million life-years realized as of 2014.

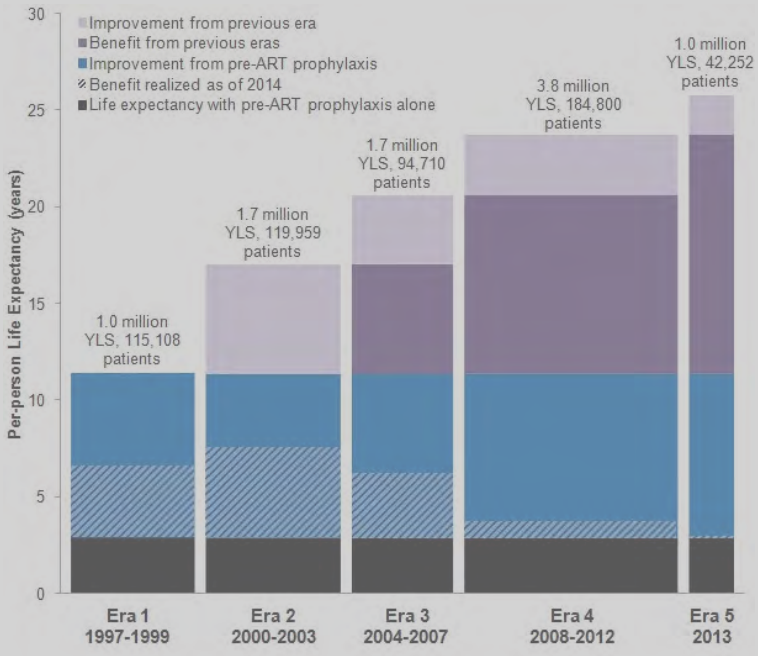


Figure 1. Years of life saved per person in each era produced by model simulations with a mean age at treatment initiation of 37 years (SD, 10 years). Bar width corresponds to the number of patients in each era and total colored area corresponds to lifetime survival benefits. Survival benefits realized as of 2014 are shaded with diagonal lines.

Conclusions: Brazil's national policy of free-of-charge ART access to patients has led to dramatic survival benefits, the vast majority of which have yet to be realized. Earlier HIV diagnosis, increased numbers accessing care, and improvements in ART regimens have all contributed substantially to these benefits.

1110 The Cost-Effectiveness of Early ART Initiation in South Africa: A Quasi-Experiment

Jacob Bor[1]; Ellen Moscoe[2]; Natsayi Chimbindi[3]; Kobus Herbst[3]; Kevindra K. Naidu[3]; Frank Tanser[3]; Deenan Pillay[3]; Till Barnighausen[3]

[1]Boston University School of Public Health, Boston, MA, US; [2]Harvard School of Public Health, Boston, MA, US; [3]Wellcome Trust Africa Centre for Health and Population Studies, Somkhele, South Africa

Background: Clinical trials are not well suited to evaluate the effectiveness and cost-effectiveness of interventions in "real world" settings. Using a quasi-experimental regression-discontinuity design (Bor et al. 2014), we establish the causal effect of early (vs. deferred) ART initiation on patient survival in rural South Africa, and obtain empirical (as opposed to modeled) cost-effectiveness estimates.

Methods: Demographic data from a large population surveillance in rural KwaZulu-Natal were linked to clinical records from South Africa's public sector ART program. 4391 patients enrolled in HIV care between 2007 and 2011. CD4 counts were collected upon entry into care regardless of ART initiation. Subjects were eligible for ART if CD4 < 200 cells/μL, as per national guidelines during this period. Dates of death were obtained from the demographic surveillance; dates of initiation and follow-up CD4 counts were obtained from clinical records. Patients were followed for up to five years. We estimated the causal effect of immediate ART eligibility on survival, immune health, and time spent in pre-ART and on ART, which were used to estimate costs. Effects were estimated using a regression-discontinuity design, which exploits the quasi-random nature of treatment assignment for patients with first CD4 counts close to the eligibility threshold. Patients just above vs. just below the threshold are similar on all observed *and unobserved* factors; but they receive different treatment assignments.

Results: Patients presenting with a CD4+ count just below 200 cells/μL were 4.3% points (95% CI 0.6, 8.0) more likely to be alive at two years compared to patients presenting with a CD4+ count just above the cut-off, an advantage that persisted at five years (Fig 1). These effects imply a 14.9% point two-year survival advantage for patients who actually initiated ART because they had an eligible CD4+ count. Large, persistent gains in clinical immune function were also observed among patients who were ART eligible. Over a five-year horizon, the additional medical care provided to ART-eligible patients implied a cost of $1967 per life year saved compared to treating patients with CD4+ counts close to 200 cells/μL.

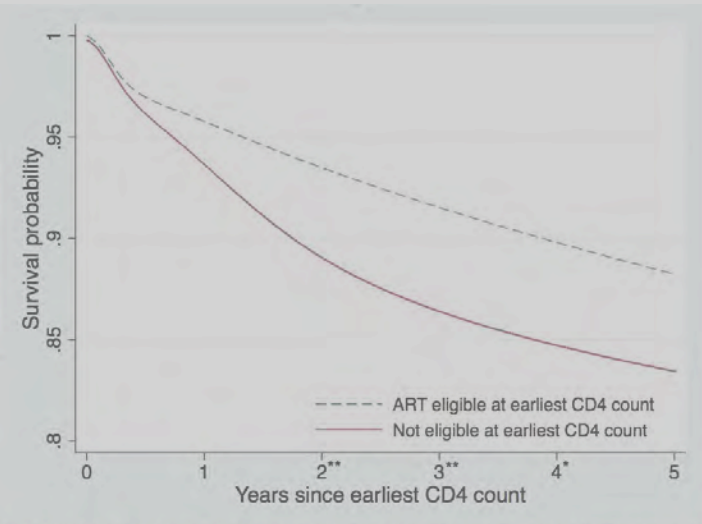


Fig 1. Predicted survival curves for patients with first CD4 counts just below (eligible) and just above (not eligible) the 200-cell threshold. Survival curves were estimated based on flexible-parametric survival models, adapted for use in regression discontinuity designs.

Reference: Bor J, Moscoe E, Mutevedzi P, Newell ML, Bärnighausen T. Regression discontinuity designs in epidemiology: causal inference without randomized trials. Epidemiology. 2014 Sep; 25(5):729-37.

Conclusions: In a real-world setting, referral of patients to pre-ART care (vs. immediate ART eligibility) led to large losses of life and health. These losses could have been avoided with immediate ART, which was found to be "very cost effective" at conventional benchmarks.

1111 Community-Based Strategies to Strengthen the Continuum of HIV Care Are Cost-Effective

Jennifer A. Smith[1]; Monisha Sharma[2]; Carol Levin[2]; Jared Baeten[2]; Heidi van Rooyen[3]; Connie Celum[2]; Timothy Hallett[1]; Ruanne V. Barnabas[2]

[1]Imperial College London, London, United Kingdom; [2]University of Washington, Seattle, WA, US; [3]Human Sciences Research Council, Sweetwaters, South Africa

Background: Closing gaps in the continuum of HIV care is a priority for public health strategies that aim to reduce HIV-associated morbidity, mortality and HIV incidence. Facility-based HIV counselling and testing (HTC) has achieved limited testing coverage and linkage to care, particularly among asymptomatic persons. Home HTC and linkage to care achieved high testing coverage and linkage to care in KwaZulu-Natal, South Africa, but its impact on population-level health and cost-effectiveness compared to existing facility-based testing has not been evaluated.

Methods: We developed an individual-based HIV transmission model parameterized with epidemiologic and cost data from home HTC and linkage studies in rural KwaZulu-Natal, South Africa. The HTC and linkage studies measured the change in the proportion of all HIV-positive persons with suppressed viral load between study enrolment and 12 months. The model simulated the intervention impact and projected the effect on health outcomes over 10 years. The incremental cost-effectiveness ratios (ICERs) were calculated for the intervention relative to existing facility-based testing per HIV incident infection and disability adjusted life year (DALY) averted.

Results: With the high coverage (91%) and linkage to ART (80%) observed in the home HTC studies, HIV-associated disability and incident infections were reduced compared to current testing modalities, especially at higher ART initiation criteria: as the ART initiation threshold increased from ≤200 cells/mm^3 to universal eligibility, 10-22% of DALYs and 11-48% of HIV infections were averted over ten years. Home HTC is "very cost effective" by WHO standards across all ART initiation thresholds: US$1,080, $925, $985 and $1,150 per DALY averted and $7,000, $7,580, $7,100 and $6,560 per infection averted with ART initiation at ≤200 cells/mm^3, ≤350 cells/mm^3, ≤500 cells/mm^3 and universal eligibility, respectively. ART costs exceeded all other costs, accounting for 48-85% of total programme costs; with universal eligibility and a reduced ART cost, the ICER per DALY averted is reduced four-fold.

Conclusions: Home HTC can strengthen linkage to care and enhance the increases in ART uptake that will result from South Africa's expanding ART eligibility criteria. As treatment programs move forward to implement '90% of HIV-infected persons tested, 90% treated, 90% achieving viral load suppression', insights from this analysis find that community-based HTC and linkage is a cost-effective strategy for HIV prevention.

1114 Global Fund Cost Projections for Implementing WHO 2013 Guidelines

Obinna Onyekwena; Ade Fakoya; Michael Johnson; Michael Olszak-Olszewski; Mark Dybul

The Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland

Background: Although recent global cost estimates indicate overall investments needed for implementation of the World Health Organization 2013 consolidated ART guidelines, detailed financial estimates for individual countries are limited. The aim of this study was to estimate additional costs for the transition of Global Fund grants to implement ART eligibility recommendations of the new guidelines.

Methods: The thirty-two countries which represent 83% of current Global Fund country allocations for HIV were included in the review. Data on treatment targets, ARV costs, and financing contributions to ARV were extracted from the Global Fund reporting database, grant documents and National AIDS Spending Assessment reports. Global projections for additional numbers of persons eligible for treatment, reported by WHO, were applied to country treatment targets to derive country-level number projections for 2015 to 2017. A weighted average ARV cost was used to determine associated ARV cost projections. Due to inter-program variability, facility and adherence support costs were not included. Treatment numbers and cost projections were disaggregated by new eligibility criteria and compared to current total allocations for HIV.

Results: ARV medicine cost for 2014 Global Fund commitments in 32 countries was estimated to be $628 million for 5 million patients on antiretroviral treatment. Additional cost of ARV medicines expected from ART eligibility recommendations was projected to be US$695 million to the end of 2017, for an additional 1.7 million persons on treatment. Costs for implementation of Option B+ and treating all HIV positive children below the age of five were US$53 million and US$106 million respectively; while initiating HIV positive persons with a CD4 count between 350 and 500 cells per mm^3 and in serodiscordant relationships had estimated additional costs of US$294 million and US$242 million respectively. The total ARV medicine cost projections represented approximately 41% (US$2.6 billion) of the total HIV allocations projected from 2015 to 2017 for the 32 countries analysed.

Conclusions: ARV medicine scale up costs alone will account for a significant portion of HIV resources allocated by the Global Fund to national HIV programs. This does not take into account additional facility and adherence support costs needed for quality service delivery. Understanding differential cost data in the implementation of treatment guidelines should strengthen strategic investments and portfolio optimisation.

Session O-10 Oral Abstracts — Room 6C

4:00 pm – 6:15 pm

New Antiretroviral Agents, Strategies, and HIV Drug Resistance

113LB Tenofovir Alafenamide (TAF) in a Single-Tablet Regimen in Initial HIV-1 Therapy

David Wohl[1]; Anton Pozniak[2]; Melanie Thompson[3]; Edwin DeJesus[4]; Daniel Podzamczer[5]; Jean-Michel Molina[6]; Gordon Crofoot[7]; Christian Callebaut[8]; Hal Martin[8]; Scott McCallister[8]

[1]University of North Carolina, Chapel Hill, NC, US; [2]Chelsea and Westminster Hospital, NHS Foundation Trust, London, United Kingdom; [3]AIDS Research Consortium of Atlanta, Atlanta, GA, US; [4]Orlando Immunology Center, Orlando, FL, US; [5]Hospital Universitari de Bellvitge, Barcelona, Spain; [6]Hopital Saint Louis, Paris, France; [7]Gordon Crofoot Research, Houston, TX, US; [8]Gilead Sciences, Inc, Foster City, CA, US; [9]Gilead Sciences, Inc, Foster City, CA, US

Background: Tenofovir alafenamide (TAF) is a novel tenofovir (TFV) prodrug that, when administered in the single tablet regimen elvitegravir/cobicistat/emtricitabine/TAF (E/C/F/TAF), has >4-fold increase in intracellular TFV diphosphate and >90% lower plasma TFV levels compared to tenofovir disoproxil fumarate (TDF). Two Phase 3 studies of identical design were conducted in distinct geographic areas comparing 2 single tablet regimens, E/C/F/TAF and E/C/F/TDF, in treatment-naïve HIV-1^+ adults.

Methods: Patients were randomized 1:1 to receive a single tablet regimen of E/C/F/TAF or E/C/F/TDF once daily in two Phase 3 double blind studies. Primary endpoint was Week 48 virologic response by FDA Snapshot algorithm in a pre-specified analysis of the combined studies.

Results: 1,733 subjects were randomized and treated: 15% women, 43% non-White, 23% viral load ≥100,000 copies/mL. Median baseline characteristics were: age 34 yrs, VL 4.58 $\log_{10}$c/mL, and CD4 count 427 cells/μL. The primary objective was met, as E/C/F/TAF was non-inferior to E/C/F/TDF with 92% and 90%, respectively, having HIV RNA <50 copies/mL at week 48 (difference +2%, 95% CI -0.7% to +4.7%, p=0.13). The rates of virologic success between E/C/F/TAF and E/C/F/TDF were similar across subgroups according to age, sex, race, baseline HIV1 RNA level, baseline CD4 cell count, region (US versus exUS), and study drug adherence. Mean change in CD4 count at Week 48 was 230 cells/μL in the E/C/F/TAF arm vs. 211 cells/μL for E/C/F/TDF (p=0.02). Virologic failure with resistance occurred in 0.8% in the E/C/F/TAF arm and 0.6% on E/C/F/TDF. Treatment related SAEs were rare: E/C/F/TAF 0.3% (n=3), E/C/F/TDF 0.2% (n=2). There were no reports of proximal renal tubulopathy (including Fanconi Syndrome) in either arm. No single AE led to discontinuation of more than 1 subject on E/C/F/TAF. Grade 2, 3, or 4 AEs occurring in ≥ 2% were: diarrhea (3.3% vs. 2.5%), nausea (2.2% vs. 2.0%), headache (2.9% vs. 2.1%), and URI (3.6% vs. 3.1%) in the E/C/F/TAF and E/C/F/TDF arms, respectively.

	E/C/F/TAF (n=866)	E/C/F/TDF (n=867)	p-value	Difference in Percentage (95% CI)
HIV-1 RNA < 50 at Week 48	800 (92.4%)	784 (90.4%)	0.13	2.0% (-0.7% to 4.7%)
Virologic Failure at Week 48	31 (3.6%)	35 (4.0%)		
HIV-1 RNA > 50	20 (2.3%)	23 (2.7%)		
Discontinued/lack of efficacy	2 (0.2%)	3 (0.3%)		
Discontinued/other, last VL > 50	8 (0.9%)	8 (0.9%)		
Added new ARV	1 (0.1%)	1 (0.1%)		
No data in window	35 (4.0%)	48 (5.5%)		
Discontinued due to AE/death	8 (0.9%)	14 (1.6%)		
Discontinued/other, last VL < 50	21 (2.4%)	31 (3.6%)		
Missing data/on study drug	6 (0.7%)	3 (0.3%)		
Virologic failure with drug resistance	7 (0.8%)	5 (0.6%)		

Conclusions: Through 48 weeks of treatment, high virologic response rates were seen in patients receiving E/C/F/TAF or E/C/F/TDF, and similar responses were seen across subgroups evaluated. Drug resistance was <1%. Both regimens were well tolerated, and no unique AEs associated with TAF occurred. These data support the use of E/C/F/TAF, the first TAF-based single tablet regimen, as a potential new regimen for initial treatment of patients with HIV-1 infection.

114LB Antiviral Activity/Safety of a Second-Generation HIV-1 Maturation Inhibitor

Carey Hwang[1]; Dirk Schürmann[2]; Christian Sobotha[2]; Heather Sevinsky[1]; Palanikumar Ravindran[1]; Hong Xiao[1]; Neelanjana Ray[1]; Mark Krystal[3]; Ira B. Dicker[3]; **Max Lataillade**[3]
[1]Bristol-Myers Squibb, Princeton, NJ, US; [2]Charité Research Organisation GmbH, Berlin, Germany; [3]Bristol-Myers Squibb, Wallingford, CT, US

Background: BMS-955176 is a 2nd-generation HIV-1 maturation inhibitor (MI). A 1st generation MI (bevirimat) showed clinical efficacy in early-phase studies, but ~50% of subjects had reduced viral susceptibility associated with naturally occurring polymorphisms in Gag. We assessed BMS-955176 antiviral activity, safety, and exposure–response during 10 days of monotherapy in HIV-1, subtype B-infected subjects.

Methods: AI468002 (NCT01803074) is a Phase 2a, randomized, multi-part trial. Forty HIV-1, subtype B-infected subjects with HIV-1 RNA ≥5000 c/mL and CD4+ T-cell counts ≥200 cells/μL were randomized 1:1:1:1 to BMS-955176 dose groups of 5, 10, 20 or 40 mg, then 4:1 to receive an oral suspension of BMS-955176 or placebo once daily (QD) for 10 days. Twenty additional subjects were later randomized to 80 and 120 mg QD dose groups. The primary endpoint was change in HIV-1 RNA from baseline to Day 11; safety and exposure–response were secondary endpoints.

Results: Overall, 60 subjects were randomized to receive either BMS-955176 (n=48) or placebo (n=12). Median change in HIV-1 RNA from baseline to Day 11 ranged from –0.15 to –1.36 $\log_{10}$ c/mL and maximum median change between baseline and Day 24 (study discharge) ranged from –0.50 to –1.70 $\log_{10}$ c/mL across the BMS-955176 groups. An exposure–response relationship was observed; there was an increase in maximum median response over the range of 5–40 mg QD, which plateaued at ~–1.64 $\log_{10}$ c/mL at doses of 40–120 mg QD. Maximum median declines in HIV-1 RNA were similar for the 40–120 mg QD dose groups regardless of baseline Gag polymorphisms (positions evaluated: V362, Q369, V370, and T371). BMS-955176 was generally well tolerated at all doses. There were no deaths, serious adverse events (SAEs), AEs leading to discontinuation, grade 3–4 related AEs or clinically relevant grade 2–4 laboratory abnormalities.

Conclusions: BMS-955176 achieved maximum median declines of >1 $\log_{10}$ c/mL in HIV-1 RNA at doses of 20–120 mg QD. Response increased with doses up to 40 mg QD, with a plateau of ~–1.64 $\log_{10}$ c/mL observed at 40–120 mg QD. The greatest response achieved was a maximum median change of –1.70 $\log_{10}$ c/mL in the 40 mg group. Unlike 1st-generation MIs, in this proof-of-concept study BMS-955176 showed similar antiviral activity in subjects with wild-type HIV-1 or HIV-1 with Gag polymorphisms. BMS-955176 was generally well tolerated at all doses. Phase 2b studies for BMS-955176 will begin Q2, 2015.

115LB Early ART and IPT in HIV-Infected African Adults With High CD4 Count (Temprano Trial)

Christine Danel[1]; Raoul Moh[2]; Delphine Gabillard[1]; Anani Badje[4]; Jerome Le Carrou[1]; Gerard M. Kouame[4]; Jean Baptiste Ntakpe[4]; Hervé Ménan[3]; Serge Eholie[2]; Xavier Anglaret[1]
On behalf of the Temprano Study Group
[1]Inserm, Bordeaux, France; [2]Université Felix Houphouet Boigny, Abidjan, Côte d'Ivoire; [3]CHU de Treichville, Abidjan, Côte d'Ivoire; [4]Programme PACCI, Abidjan, Côte d'Ivoire

Background: We present the final results of the Temprano ANRS 12136 trial that assessed the benefits of early ART and/or early 6-month isoniazid prophylaxis (IPT, 300 mg/day) among HIV-infected adults with high CD4 counts and no WHO criteria for starting ART.

Methods: Temprano was a randomized 2x2 factorial superiority trial conducted in 9 HIV care centers in Côte d'Ivoire from March 2008 through January 2015. Inclusion criteria were: HIV-1 infection, age ≥18 years, CD4 nadir ≤800/ul, and no criteria for starting ART according to the most recent WHO guidelines. Participants were randomized to one of four arms: ART initiation according to WHO criteria (WHOART); immediate 6-month IPT plus ART initiation according to WHO criteria (WHOART-IPT); immediate ART initiation (EarlyART); immediate 6-month IPT plus immediate ART initiation (EarlyART-IPT). First-line ART consisted of tenofovir plus emtricitabine plus either efavirenz, zidovudine or lopinavir/ritonavir. The primary endpoint was severe HIV morbidity (AIDS-defining diseases, non-AIDS-defining malignancy, or non-AIDS-defining invasive bacterial diseases),or any-cause mortality at 30 months. The secondary endpoint was any other grade 3-4 defining morbidity. We used multivariate Cox proportional models to compare outcomes between the WHOART and EarlyART arms, and between the IPT and no IPT arms. We tested for interaction between earlyART and IPT.

Results: Of 2,076 patients randomized, 2,056 were included in the analysis (78% were women; 91% classified at WHO stage 1-2; median age 35 years; median CD4 nadir 465/ul; median HIV-1 viral load 4.7 $\log_{10}$ copies/ml). They were followed for 4,755 patient-years, during which 47 died, 175 experienced 204 episodes of severe morbidity (TB 85, invasive bacterial diseases 56, other AIDS-defining diseases 11, non-AIDS malignancy 5), 287 experienced 364 episodes of severe grade 3-4 morbidity (hematologic 256, hepatic 31 renal, 22, cardiovascular 9, others 46), and 44 (2.2%) were lost-to-follow up. There was no interaction between EarlyART and IPT. The risk of severe morbidity was 44% lower with EarlyART vs. WHOART (Table) and 35% lower with IPT vs. no IPT. EarlyART significantly decreased morbidity overall and when restricted to patients with baseline CD4 >500/ul. The risk of Grade 3-4 morbidity did not differ between strategies.

Severe morbidity	N	TAR (PY)	Rate (/100PY)	AHR	(95% CI)
Overall					
WHOART	111	2,247	4.94		
EarlyART	64	2,310	2.77	0.56	(0.41 - 0.76)
No IPT	104	2,225	4.67		
IPT	71	2,332	3.04	0.65	(0.48 - 0.88)
Baseline CD4 >500/ul					
WHOART	38	918	4.14		
EarlyART	23	964	2.39	0.56	(0.33 - 0.93)
No IPT	37	918	4.03		
IPT	24	965	2.49	0.61	(0.37 - 1.02)

N: number of events. PY: person-years; TAR: time at risk; AHR: adjusted hazard ratio; CI: confidence interval

Conclusions: In Côte d'Ivoire, both immediate ART and IPT dramatically and independently decreased the risk of severe morbidity, and should be recommended as the standard of care for HIV.

116 Antiretroviral Drug Screening Provides Key Insights Into HIV Drug Resistance

Iris Chen[1]; Matthew B. Connor[2]; William Clarke[1]; Mark A. Marzinke[1]; Vanessa Cummings[1]; Sheldon D. Fields[3]; Darrell P. Wheeler[4]; Kenneth H. Mayer[5]; Beryl A. Koblin[6]; Susan H. Eshleman[1]
[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [3]Florida International University, Miami, FL, US; [4]Loyola University Chicago, Chicago, IL, US; [5]Fenway Health, Boston, MA, US; [6]New York Blood Center, New York, NY, US

Background: The HIV Prevention Trials Network (HPTN) 061 study enrolled HIV-infected and HIV-uninfected Black men who have sex with men in six cities in the United States who were at a high risk of HIV infection. Most of the HIV-infected men in the study reported that they were unaware of their HIV status or that they were aware of their status but were not in care. HIV drug resistance was detected in 48 (28.4%) of 169 HIV-infected men who were not virally suppressed at study enrollment. We used a high-throughput assay to screen for the presence of antiretroviral (ARV) drugs in samples from these study participants.

Methods: Plasma samples were obtained at the HPTN 061 enrollment visit from the 169 HIV-infected men described above. Samples were tested for the presence of 15 ARV drugs using a qualitative assay based on high-resolution mass spectrometry. Self-reported data on prior and current ARV drug use for pre-exposure prophylaxis, post-exposure prophylaxis, and ARV treatment were collected in the HPTN 061 study.

Results: ARV drugs were detected in 60 (35.5%) of the 169 men, including 27 (56.3%) of the 48 men who had drug-resistant HIV. Eighteen (37.5%) of those 48 men had at least one ARV drug detected that was not consistent with their drug resistance mutations. Unusual combinations of ARV drugs were detected in some samples. Thirty-one of the 137 men who reported no prior or current ARV drug use had drug-resistant HIV; based on these data alone (self-reported ARV drug use and resistance testing), the estimated rate of transmitted drug resistance (TDR) was 22.6%. However, 14 of the men with drug-resistant HIV also had at least one ARV drug detected. After excluding those men, the estimated rate of TDR was 12.4%. Five (29%) of the 17 men with TDR had multi-class drug resistance.

Conclusions: ARV drug testing can provide important information relevant to the emergence and transmission HIV drug resistance. In addition to the high levels of drug resistance previously observed in this cohort, ARV drug testing indicated that a significant portion of the men were at risk of acquiring additional drug resistance mutations. ARV drug testing also provided a more accurate estimate of TDR by identifying men who were using ARV drugs but chose not to disclose this to study staff. These findings demonstrate the benefit of combining HIV drug resistance testing with ARV drug testing for the analysis of HIV drug resistance.

117 Untimed Drug Levels and Resistance in Patients Experiencing Low-Level HIV Viremia

Alejandro Gonzalez-Serna; Luke C. Swenson; Adriana Nohpal; Birgit Watson; Kate Auyeung; Julio Montaner; Richard Harrigan
BC Centre for Excellence in HIV/AIDS, Vancouver, Canada

Background: HIV resistance testing in HAART patients experiencing low-level viremia (LLV, 50-999 HIV-RNA copies/mL) predicts the risk of subsequent virologic failure (VF, ≥1000 copies/ml). Suboptimal plasma drug levels can arise as a result of poor adherence and/or pharmacokinetic issues. Here, our aim was to evaluate whether retrospective analysis of plasma levels also provides insight into patient outcomes after experiencing LLV.

Methods: The first documented LLV episode of 2176 patients was analyzed. A total of 328 consenting patients with drug levels, genotypic resistance data and with follow-up clinical data while on constant therapy available were eligible. Untimed plasma drug levels (UDL) of PIs and NNRTIs in the sample corresponding to the first LLV episode were measured by HPLC-tandem MS. Drug levels were categorized as 'therapeutic' or 'suboptimal' based on target trough concentrations from DHHS guidelines. Resistance was assessed using the Stanford algorithm (GSS, corresponding to the number of 'active' drugs prescribed). Time to VF after LLV was evaluated by Kaplan–Meier analysis and Cox proportional hazards regression.

Results: 78 of 328 patients (24%) had suboptimal drug levels at LLV, compared with 63 (19%) having GSS<3. Both suboptimal UDL and GSS<3 independently increased the risk of future pVL >1000. Within a year, 56/78 (72%) patients with suboptimal UDL had failed, compared to 45/63 (71%) with GSS <3 and to 103/206 (50%) with both optimal GSS and UDL. Of those with suboptimal UDL, 43/78 (55%) had undetectable levels of PI/NNRTI, with most (81%) failing by one year. Only 18 patients had both suboptimal UDL and GSS<3.

In the adjusted multivariable model, variables associated with VF were suboptimal UDL (Adjusted Hazard Ratio, AHR 2.9, 95%CI 2.0-4.2, p<0.001), female gender (AHR 1.9, 95%CI 1.3-2.9, p=0.001), GSS<3 (AHR 1.5, 95%CI 0.9-2.3, p=0.098) and being HAART-naïve (AHR 1.7, 95%CI 1.1-2.7, p=0.031). When UDL and GSS categories were combined, the lowest VF was found for optimal UDL &GSS≥3 (P<0.001). Numerous sensitivity analyses confirmed these findings.

Conclusions: A single untimed drug level (UDL) and GSS independently predict subsequent VF, with suboptimal UDL having a greater hazard than GSS<3, especially if drug levels are undetectable. Together, UDL and GSS can explain a higher proportion of treatment failures than either measure alone. These results could justify the potential investigation of UDL in prospective of management of LLV.

118 Pretreatment HIV Drug Resistance Increases Regimen Switch in Sub-Saharan Africa

Tamara Sonia Boender[1]; Bernice M. Hoenderboom[1]; Kim C. Sigaloff[1]; Maureen Wellington[2]; Margaret Siwale[3]; Cissy M. Kityo[4]; Alani Sulaimon Akanmu[5]; Mariette E. Botes[6]; Tobias F. Rinke de Wit[1]
On behalf of the PASER Study Group

[1]*Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands;* [2]*Newlands Clinic, Harare, Zimbabwe;* [3]*Lusaka Trust Hospital, Lusaka, Zambia;* [4]*Joint Clinical Research Centre, Kampala, Uganda;* [5]*Lagos University Teaching Hospital, Lagos, Nigeria;* [6]*Muelmed Hospital, Pretoria, South Africa*

Background: After the successful scale-up of antiretroviral therapy (ART) in Africa, there are concerns about emerging drug-resistant HIV and an increasing need for more costly second-line regimens. We investigated the impact of pretreatment drug resistance (PDR) on 2 and 3 year ART outcomes and switch to second-line in the first 3 years of ART within the Pan-African Studies to Evaluate Resistance Monitoring (PASER-M) cohort.

Methods: The PASER-M cohort followed HIV-1 infected individuals initiating first-line ART for 2 years (13 sites) or 3 years (5 sites) in 6 African countries. Viral load (VL) and *pol* genotypic testing (if VL>1000 cps/ml) was performed at ART initiation and annually thereafter. PDR was defined as a decreased susceptibility to at least one prescribed drug, using the Stanford algorithm and IAS-USA mutation list. The effect of PDR on (I) switch to second-line with acquired drug resistance, (II) virological failure (VL>400 c/ml) and (III) acquired drug resistance during the first 3 years of ART was assessed using cumulative incidence plots, multivariate cox-models and multilevel logistic regression. Unnecessary switch was defined as switch with VL<1,000 cps/ml or VL>1,000 cps/ml with wild-type virus.

Results: For 2,579 (94.2%) of 2,737 participants genotypes were available at ART initiation; in 5% (n=139) PDR was present. After 3 years, 112 (4.3%) participants had switched to second-line regimen of whom 78 (69.6%) had VL results and genotypes available; 33.3% (n=26) switched unnecessarily. Most switches with drug resistance took place after 1 year of ART (figure). Incidence density of switch was 1.1 per 100 person-years. PDR increased the risk of: (I) switch with drug resistance, subhazard ratio 7.8 (95%CI 3.9-15.6) during 3 years; (II) virological failure, odds ratios (OR) 2.9 (95%CI 1.4-5.8) after 2 years and 2.8 (95%CI 1.1-7.2) after 3 years, and (III) acquired drug resistance, OR 2.5 (95%CI 1.2-5.4) after 2 years and OR 5.0 (95%CI 1.8-14.3) after 3 years of first-line ART. PDR was not associated with mortality or new AIDS events.

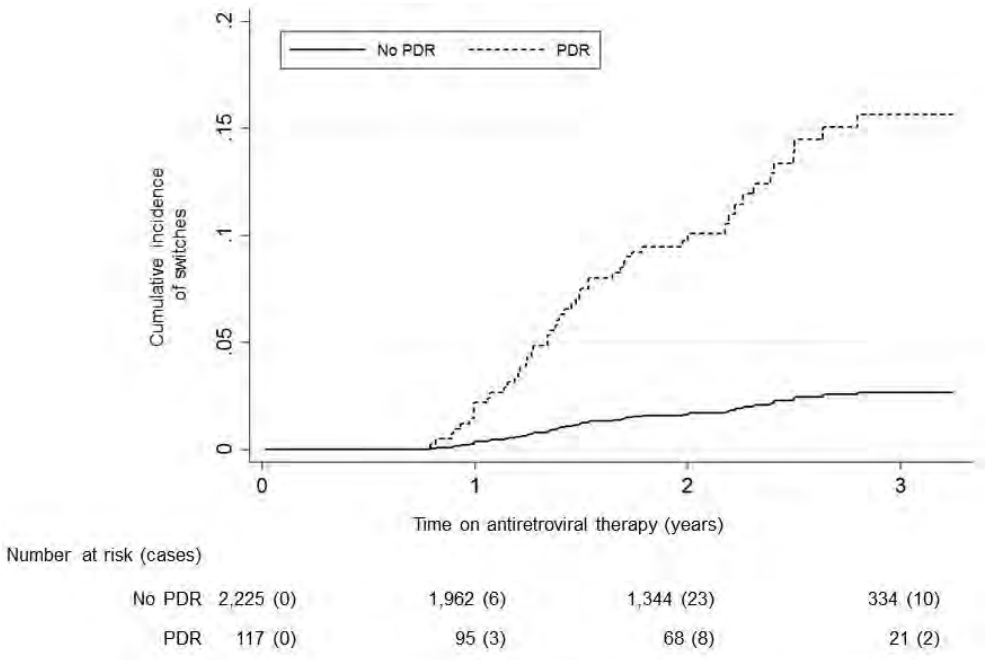


Figure. Cumulative-incidence curve of switches to second-line antiretroviral therapy, by pretreatment drug resistance (PDR).
Switch is defined as a change to second-line regimen with acquired drug resistance.

Conclusions: PDR is strongly associated with switching to second-line ART, but does not cause excess mortality or AIDS related events. VL monitoring can enable timely detection of therapy failure and avoid unnecessary switches. In view of rising PDR levels in Africa, these findings have important implications for allocation of ART resources and renders mitigating PDR a priority.

119 Impact of NRTI Cross-Resistance on Second-Line PI + NRTI Therapy Outcomes in Africa

Nicholas Paton[1]; Cissy Kityo[2]; Jennifer Thompson[5]; Leonard Bagenda[2]; James Hakim[6]; Joep van Oosterhout[4]; Andrew D. Kambugu[3]; Anne Hoppe[5]; Sarah Walker[5]
On behalf of the EARNEST Trial Team

[1]National University of Singapore, Singapore, Singapore; [2]Joint Clinical Research Centre, Kampala, Uganda; [3]Infectious Diseases Institute, Kampala, Uganda; [4]University of Malawi, Blantyre, Malawi; [5]MRC Clinical Trials Unit at University College London, London, United Kingdom; [6]University of Zimbabwe Clinical Research Centre, Harare, Zimbabwe

Background: Extensive NRTI resistance, common at the time of switch to second-line therapy in ART programme settings, is expected to affect outcomes. We examine the impact of baseline NRTI resistance on responses to PI+NRTIs in the EARNEST trial.

Methods: 1277 patients aged ≥12y who met WHO-defined treatment failure criteria after >12 months on NNRTI-based first-line ART in African rollout programmes were randomised to receive bPI (standardised to lopinavir/ritonavir 400mg/100mg bd) with either 2/3 NRTIs selected by clinician based on algorithms without resistance testing (PI/NRTI); with raltegravir (RAL 400mg bd)(PI/RAL), or as monotherapy (+RAL induction for first 12 weeks)(PI-mono). PI-mono was stopped after 96 weeks; other groups continued randomised treatment to week 144. Drug resistance at baseline (done in 391/426 in PI/NRTI) and VL during study were tested retrospectively on stored samples (results blinded during trial).

Results: Patients had advanced treatment failure (42% VL≥100,000 c/ml, 62% CD4<100 cells/mm^3) at baseline. In PI/NRTI, 80% received TDF+3TC/FTC (±ZDV). Based on resistance testing, the PI/NRTI regimen contained 0 predicted active NRTIs (at most low-level resistance, Stanford criteria) in 230 (59%, PI/NRTI(0)), 1 active NRTI in 128 (33%, PI/NRTI(1)) and ≥2 active NRTIs in 33 (8%, PI/NRTI(2)). VL suppression in PI/NRTI(0) was markedly superior to PI-mono (76% vs 44% respectively <50 c/ml at week 96; P<0.001), and similar to PI/RAL (76% vs 72% <50 c/ml for PI/NRTI(0) and PI/RAL respectively at week 144, P=0.28, Figure). Response in PI/NRTI(1) was identical to PI/NRTI(0) (both 76% < 50 c/ml at week 144; P=0.92) but slightly lower in PI/NRTI(2) (62% < 50 c/ml; P=0.12 vs PI/NRTI(1)).

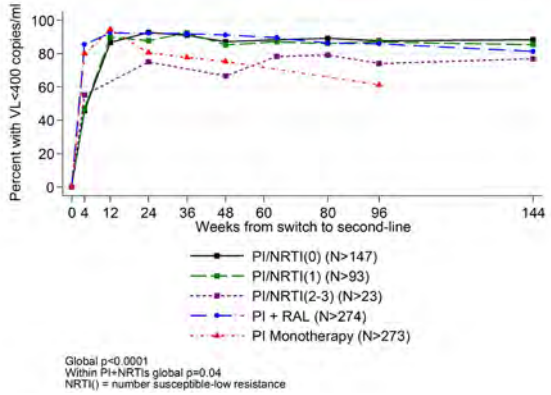


Figure: VL suppression in PI/NRTI arm by genotype-predicted NRTI activity, compared to supression in PI/RAL and PI-mono arms

Conclusions: Even when there is little or no predicted activity due to resistance, NRTIs make a major contribution to efficacy of PI/NRTI second-line therapy with clear added activity over the PI alone, equivalent to adding a drug from a new class. No difference between 0 and 1 active NRTIs suggests this contribution is not due to direct drug activity (possibly represents a viral fitness effect). The paradoxical trend to worse outcome with 2 active NRTIs may reflect a small group of patients with very poor adherence on first-line, continued during second-line. Algorithmic NRTI drug selection and attention to adherence are likely to achieve optimal outcomes in standardised PI/NRTI second-line therapy in resource-limited settings with resistance testing to select NRTIs of little added value.

120 Fitness Effects of Drug-Resistant Strains Across the United States HIV-1 Transmission Network

Joel O. Wertheim[1]; Alexandra M. Oster[2]; Neeraja Saduvala[2]; Walid Heneine[2]; Jeffery A. Johnson[2]; William M. Switzer[2]; Angela L. Hernandez[2]; H. Irene Hall[2]

[1]University of California San Diego, San Diego, CA, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: Drug resistance associated mutations (DRAMs) can reduce the effectiveness of antiretrovirals (ARVs). DRAMs from multiple drug classes can have deleterious effects on intrahost viral fitness (replication) and may reduce transmissibility. We used genetic transmission network analysis to assess the effect of DRAMs on interhost viral fitness (transmission, or network links).

Methods: We analyzed 66,235 HIV-1 *pol* sequences reported to the US National HIV Surveillance System for persons diagnosed through 2012; 30,200 were collected within 3 months of diagnosis in ARV-naïve persons. We aligned all sequences to a reference sequence (HXB2), removed DRAM-associated codons, and constructed a transmission network by linking sequences with ≤1.5% Tamura-Nei genetic distance, indicating potential transmission between two persons. Among ARV-naïve persons, we determined the percentage that clustered with ≥1 sequence, by presence of DRAMs, overall and by drug class, and conducted multivariable analysis to account for potential confounders.

Results: Of 30,200 ARV-naïve persons, 12,539 (42%) clustered. Protease and non-nucleoside reverse transcriptase inhibitor DRAMs were not associated with clustering. However, nucleoside reverse transcriptase inhibitor (NRTI) DRAMs were associated with reduced clustering (33% with NRTI DRAMs clustered vs. 42% without NRTI DRAMs, $p<0.0001$). After adjusting for age, race/ethnicity, transmission category, geographic region, and diagnosis year, having NRTI DRAMs was still associated with reduced clustering. No single mutation appears responsible for the reduced clustering. M184V, which has known deleterious intrahost fitness consequences, was associated with a lower prevalence of clustering (18%) and was present in only 8% of persons with an NRTI DRAM. Persons in the 7 largest DRAM clusters (≥30 person, ≥90% sharing a mutation) did not differ significantly from those in the 26 largest non-DRAM clusters (≥30 person) with respect to sex, race/ethnicity, or transmission category. However, persons in DRAM clusters were significantly more likely to be diagnosed in the last 3 years of the analysis period. These DRAM clusters contained mutations from all three drug classes.

Conclusions: With the exception of NRTI mutations, DRAMs did not have deleterious effects on interhost transmission. Our findings likely reflect compensatory mechanisms that improve fitness or insignificant impact of DRAMs on transmissibility and highlight the propensity for drug-resistant HIV-1 to spread.

121 Dolutegravir Resistance Requires Multiple Primary Mutations in HIV-1 Integrase

Arne Frantzell; Christos J Petropoulos; **Wei Huang**

Monogram Biosciences, South San Francisco, CA, US

Background: HIV-1 integrase sequences containing mutations at positions 143, 148 and 155 represent major resistance pathways to integrase inhibitors (INI). These genetic pathways are generally distinct for raltegravir and elvitegravir; the emergence of more than one primary mutation in a single virus genome is rarely observed. In a clinical trial, the viruses of four of seven virologic failure cases treated with a dolutegravir (DTG) based regimen contained combinations of mutations at positions 143, 148 and 155. To understand how the combined effects of primary mutations enable HIV to escape DTG drug pressure, we examined the impact of combinations of primary mutations on DTG susceptibility and replication capacity, with and without additional secondary mutations.

Methods: A series of laboratory viruses containing site directed mutations at HIV-1 integrase positions 143, 148 and 155 alone, in combination, or with secondary mutations T97A or G140S, were constructed. INI susceptibility and replication capacity (RC) were determined using a pseudovirus luciferase reporter assay.

Results: Single mutations at positions 143, 148 or 155 alone did not confer reductions in DTG susceptibility. Double mutations Y143R+N155H and Q148H+N155H produced modest reductions in DTG susceptibility (FC=3.1, 4.2, respectively), whereas the Y143R+Q148H double mutations did not (FC=0.7). The addition of G140S, a Q148 pathway mutation, to the double mutants Y143R+Q148H and Q148H+N155H further reduced DTG susceptibility (FC=6.2, 35, respectively) and fully restored the RC of the Y143R+Q148H and Q148H+N155H viruses (RC=17%, 3%, respectively). In contrast, the addition of G140S dramatically decreased the RC of the Y143R+N155H mutant from 60% to 5%. The addition of T97A, a Y143 or N155 pathway mutation, to the Y143R+N155H mutant did not confer a further reduction in DTG susceptibility, but did reduce RC.

Conclusions: This study demonstrates that HIV-1 variants containing combinations of INI resistance mutations at positions 143, 148 and 155 exhibit reduced susceptibility to DTG. Viruses that harbor mutations belonging to the 148+155 escape pathway are less susceptible to DTG and exhibit similar or greater RC than viruses harboring mutations belonging to the 143+148 or 143+155 pathways. Thus, in the face of DTG pressure, HIV-1 variants with 148 and 155 mutations likely possess a replication advantage over variants with 143 and 148 mutations or 143 and 155 mutations.

Session S-4 Symposium — Room 613

4:00 pm – 6:00 pm

Making Sense of Sensing: Innate Immunity and HIV Infection

122 Role of Tetherin in the Evolution and Spread of HIV-1

Daniel Sauter

Ulm University Medical Center, Ulm, Germany

The interferon-inducible protein tetherin (also known as BST-2 or CD317) has emerged as a key component of the intrinsic immunity against retroviruses. Initially, tetherin was shown to restrict HIV-1 in the absence of the viral protein U (Vpu) by inhibiting the release of budding virions from infected cells. More recently, it has become clear that tetherin also acts as a pattern recognition receptor inducing NF-κB-dependent expression of antiviral and proinflammatory genes in HIV infected cells. Notably, tetherin does not only restrict retrovirus release but has activity against diverse enveloped viruses including Arena-, Filo- and Herpesvirues. Whereas the ability to restrict virion release is highly conserved among mammalian tetherin orthologs and probably an ancient function of this protein, innate sensing seems to be unique to the human and chimpanzee orthologs and thus an evolutionarily recent activity. The potent and broad antiviral activity of tetherin has driven the evolution of antagonists in many viruses. Simian (SIV) and human immunodeficiency viruses, for example, use at least three different proteins (Nef, Vpu or Env) to antagonize tetherin. The continuous arms race of tetherin with viral antagonists is probably also the reason for a unique deletion in the cytoplasmic tail of human tetherin that renders it resistant against SIV Nef. Since most SIVs - including the direct precursors of HIV-1 - use Nef to antagonize tetherin in their respective hosts, human tetherin poses a significant barrier to successful cross-species transmissions to humans. Interestingly, the four groups of HIV-1 (M, N, O and P) which arose from independent cross-species transmissions, have evolved different mechanisms to overcome this hurdle. Whereas pandemic HIV1 group M viruses switched from Nef to Vpu to counteract human tetherin, rare group P and N Vpus do not or only poorly antagonize this restriciton factor. In contrast, Nef

proteins of epidemic HIV1 group O viruses target a region adjacent to the deletion in human tetherin to increase virion release from infected CD4+ T cells. Thus, potent tetherin counteraction may be a prerequisite for the efficient spread of lentiviruses in the human population. The coevolution of tetherin with primate lentiviruses, the molecular mechanisms underlying its antagonism and implications for spread and pathogenesis of human immunodeficiency viruses will be presented.

123-A Innate Sensing of HIV-1 in Macrophages

Martin R. Jakobsen

Aarhus University, Aarhus C, Denmark

Given the important role of cytosolic DNA in stimulating innate immune responses, there is an intense interest in defining the sensors of HIV DNA and the cellular mechanisms underlying subsequent induction of Interferon (IFN). The innate immune response is orchestrated in a complex manner where various pathogen recognition receptors scavenge for pathogen associated molecular patterns. Within the last years our understanding of how HIV is sensed by immune cells has increased significantly. The major break-through was the identification of cyclic GMP-AMP (cGAMP) synthetase (cGAS) as the innate sensor of foreign DNA. Activation of cGAS initiates the production of cGAMP, which in turn acts as the second messenger binding to the ER-bound protein STING and triggering IFN production. The role of cGAS as the pivotal DNA sensor is very compelling and supported by in vitro data, crystal structures, and a strong phenotype of cGAS-deficient mice. Accumulating evidence suggests, however, that another DNA sensor, Interferon gamma inducible factor 16 (IFI16), also play a key role in the recognition of HIV DNA. IFI16 was originally described as a nuclear protein involved in the regulation of transcription, and chromatic remodeling. In 2010 it was shown, however, that cytosolic IFI16 is responsible for recognizing HSV-1 DNA (Unterholzner, Nature Immunology, 2010). At the same time as cGAS was described as a HIV sensor (Gao et al. Science 2013), we demonstrated that IFI16 was critical for triggering innate immune responses against HIV in macrophages and that IFI16 depletion significantly increased HIV replication (Jakobsen et al, PNAS 2013). More recent data now suggest that IFI16 may also play an essential role in the depletion of CD4+ T cells by recogniting reverse transcriptase intermediates from abortive infections, which lead to caspase-1 activation and IL-1ß release (Doitsh et al. Nature 2014).

In conclusion, IFI16 and cGAS clearly play key roles in sensing HIV, but perhaps even more importantly, we now know that recognition of HIV triggers robust antiviral and inflammatory responses, as well as cell death mechanisms that impact HIV immunopathogenesis. In this talk, I will discuss the interplay between HIV-1 infection and cytosolic PRRs recognition. Furthermore, I will touch upon new interesting functions of IFI16 in the cGAS-STING pathway and in directly suppressing HIV transcription.

124 Innate Sensing and Signaling to HIV-1 in Dendritic Cells

Teunis Geijtenbeek

Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Dendritic cells (DCs) are central players in the induction of innate and adaptive immunity to HIV-1. Innate sensing of pathogens by pattern recognition receptors (PRRs) triggers signaling pathways that lead to the induction of DC maturation, antiviral type I IFN responses and cytokine responses, and subsequent induction of specific T helper cell differentiation and adaptive immunity. It is becoming clear that early innate immune responses greatly affect susceptibility as well as chronic disease progression. Our recent data have uncovered an important role for type I IFN responses in the induction of follicular T helper cells, which can affect disease progression by inducing strong antibody responses. However, several viruses including HIV-1 have developed strategies to prevent innate sensing and/or innate signaling and identification of these mechanisms greatly facilitate development of novel strategies to combat infections. Here I will discuss the role of innate signaling by different pattern recognition receptors, including DC-SIGN and TLR8, in infection of DCs and modulation of innate and adaptive immune responses. Recent data strongly sugges that although DCs are equipped with innate sensors for HIV-1, the virus has developed various strategies to either escape or counteract sensing and induction of antiviral immunity.

125 How HIV-1 Evades DNA Sensors

Vineet KewalRamani

National Cancer Institute, Frederick, MD, US

Retroviruses must replicate their genomes in the presence of cytosolic DNA sensors capable of triggering an antiviral response. Here we demonstrate that HIV-1 reverse transcribed DNA products are shielded from cytosolic DNA sensors by the HIV-1 core. Treatment of HIV-1 infected cells with the capsid-binding drug PF-3450074 releases DNA products into the cytosol where they can stimulate the cGAS-STING pathway and produce a type I IFN response. HIV-1 coordinates reverse transcription and uncoating to minimize exposure of DNA products, and perturbation of either process can influence the ability of HIV-1 to induce a type I IFN response. Both wild-type and capsid-mutant HIV-1 isolates stimulate an antiviral response in macrophages that is dependent on viral DNA synthesis and impedes subsequent rounds of virus infection. Collectively, these results illustrate the interdependence of reverse transcription and uncoating, and the importance of coordinating these two viral activities to avoid immune stimulation.

Session S-5 Symposium — Room 6D

4:00 pm – 6:00 pm

Advancing HIV Prevention: Lessons from Biology, Medicine, and Public Health Law

126 The Biology of HIV Transmission: What We Think We Know and How We Know It

Julie M. Overbaugh

Fred Hutchinson Cancer Research Center, Seattle, WA, US

Biomedical prevention of HIV depends on blocking early events in the transmission process. Thus, designing and testing prevention strategies using appropriate model systems that mimic the biology of HIV transmission may help optimize the chances for success. There is, in fact, little direct information about the biology of HIV transmission in humans because this window is difficult to capture. However, plausible theories about this process can be inferred from studies of the properties of transmitted viruses and from early events in model systems. This lecture will discuss how these findings have helped inform our understanding of HIV transmission biology as well as the limitations of this knowledge.

127 HIV Phylogenetics: Lessons for HIV Prevention

Christophe Fraser

Imperial College London, London, United Kingdom

HIV phylogenetics, the study of viral genetic sequences, is used to track the spread of different viral lineages, and to identify likely transmission events, chains and clusters. Phylogenetics enhances HIV prevention science by quantifying the risk factors for onwards transmission, resolving epidemics into sub-epidemics, and identifying common routes of transmission. In discordant pair studies, such as HPTN 052, phylogenetics is used to determine whether transmission events could or could not have occurred within the studied couple. This increases the power and accuracy of such studies.

In concentrated epidemics, such as amongst MSM in Europe, phylogenetics has been used to characterize transmission patterns. After reviewing key results in the area, I will focus on recent phylogenetic studies conducted in the Netherlands, where the epidemic amongst MSM has been increasing in recent years. We determined the characteristics and dynamics of different transmission clusters, and found that the epidemic was diffuse, with a large number of clusters sharing similar dynamics. We find that the epidemic is continuously replenished by the formation of new clusters amongst younger individuals. Next, by zooming in on probable transmission pairs, we quantified transmission rates throughout the stages of infection, starting from acute infection and through the different stages of the care and treatment continuum. We found that HIV prevention requires a combination of improvements in take-up of testing, speedy treatment initiation, and rapid viral suppression.

I will conclude by describing next-generation sequencing data from different settings. Here, the whole viral genome is reconstructed, and a measure of diversity within samples is also obtained. Dual infection can be identified with relative ease, and is observed in all studied populations. These techniques yield large increases in phylogenetic resolution, such that sub-epidemics can be more clearly delineated. I will describe how phylogenetics is becoming part of the standard toolkit of HIV prevention studies.

All work described is joint work with the HIV Monitoring Foundation in Amsterdam, the BEEHIVE collaboration, the PANGEA-HIV consortium, the HPTN 071 study team, and my research group at Imperial College.

128 Optimizing ART: Treatment as Prevention in the US: Will It Be Enough?

Richard A. Elion

Whitman-Walker Health, Washington, DC, US

The success of treatment as prevention (TASP) for HIV has resulted in a significant reduction in rates of transmission. These declines are reflected in some municipalities as HIV incidence has diminished by upwards of 50% in some areas. These benefits have not been consistent across communities, as reflected through variable HIV suppression rates in the HIV treatment cascade in different communities. Nearly 90% viral suppression rates are seen in clinical trials, yet numerous models of HIV cascade success demonstrate viral suppression rates ranging from approximately 30% -70%. The impact of treatment as prevention is clear in cities where this approach has been widely adopted, but the declines in HIV incidence level off within 2 years and plateau.

These benefits are substantial, but inadequate if our goal is to give birth to an HIV free generation. TASP can be improved, but must be complemented by aggressive prevention services. Pre Exposure Prevention is an important adjunct, as we just can't treat our way out of the epidemic. Integration of preventive services into HIV service models is essential as we expand the model of HIV care to a community oriented primary care model. Changes in educational models that stress engagement and empowerment on a community level are essential to bring parity to emerging communities at risk for HIV and other STDs. Harm reduction strategies that treat biological consequences of behavior can offer deeper reductions in HIV through prep and sterile injections.

The final mile in the delivery of optimal suppression is the hardest and involves social and health equalities. The differing models of the cascade illustrate the role of adequate insurance and social class. Both Washington DC as typified by a well functioning community health center that has nearly 100% coverage for health insurance and the Kaiser Permanente system have near universal coverage but suppression rates that vary greatly. Access can partially explain these differences, but class and poverty contribute to mental health and substance abuse, and may serve our toughest hurdle to cross.

129 Criminalizing HIV: Recent Experience in the United States and Africa to Update Laws and Policies to Promote the Public Health

Jeffrey Crowley

Georgetown University, Washington, DC, US

Laws and policies have been used to protect people living with HIV and affected communities from stigma and discrimination. Indeed, the Americans with Disabilities Act (ADA) and the UN Convention on the Rights of Persons with Disabilities are just two legal instruments that help to create environments where people feel safe enough to come forward for HIV testing and to engage in care. Laws and policies also are used in ways that are highly stigmatizing and that hinder public health approaches to responding to HIV. In the United States, thirty-four states and territories have laws that criminalize the conduct of people living with HIV based on perceived exposure to HIV and without any evidence of intent to do harm. Far from representing a legacy of the past, people with HIV continue to be prosecuted and jailed for failure to disclose their HIV status prior to engaging in sex and for spitting and biting offenses, often in the context of arrest by law enforcement. Moreover, this is a challenge in countries across the globe. As of 2013, twenty-six African countries had overly broad and/ or vague HIV-specific criminal laws, most enacted over the past decade, with a further three countries considering new HIV-specific criminal laws. As governments, clinicians, researchers, and advocates seek to maximize population-level HIV viral suppression both to protect the health of people with HIV and also to reduce HIV transmission, these laws and policies could hinder our collective efforts. This talk will examine the current landscape of HIV criminal laws and policies in the US and selected African countries, will examine available data on the effectiveness of such laws at deterring behaviors such as failure to disclose HIV status prior to sexual encounters, and will look for common lessons from both Africa and the US to suggest a path forward for promoting effective evidence-based approaches to reducing HIV transmission.

Session S-6 Symposium — Room 6E

4:00 pm – 6:00 pm

Tuberculosis: Magic Bullets and Moving Targets

130 Advances in Mycobacterial Diagnostics

Mark P. Nicol

University of Cape Town, Cape Town, South Africa

The past 10 years have seen rapid advances in mycobacterial diagnostics. Specifically, nucleic acid amplification testing has been validated and widely implemented for both TB diagnosis and for identification of resistance to first and second line anti-TB drugs.

The World Health Organization has recommended use of Xpert MTB/RIF (Xpert) as the initial diagnostic test for TB in high HIV or drug-resistant TB settings, including testing of children and for specific forms of extra-pulmonary TB. Xpert simultaneously detects *M. tuberculosis* and identifies rifampicin resistance, has excellent specificity and improved sensitivity over smear microscopy for diagnosis of TB, but lacks sufficient sensitivity for use as a rule-out test for HIV-associated TB. Studies assessing the impact of Xpert implementation have shown mixed results, particularly where empiric treatment is common; as such treatment may reduce the impact of Xpert on case detection. The role of Xpert in reducing time to treatment, outcome and transmission of drug-resistant TB is an important area for further research.

Several other genotypic tests are now used for identification of resistance to first and second line anti-TB drugs. These detect the absence of wild-type (sensitive) sequence and/ or the presence of known resistance-conferring mutations. Line probe assays are commonly used, however targeted sequencing and whole genome sequencing are likely to be increasingly used as they provide improved specificity and broader mutation detection. Obstacles to the widespread implementation of sequencing include limited data on the genotype-phenotype relationship for many drugs, the lack of 'plug and play' pipelines for bioinformatics analysis and cost.

Gaps in the current portfolio of diagnostic tests include highly sensitive tests for the diagnosis of extra-pulmonary TB, TB in children and HIV-associated TB. There is a need for a true point-of-care diagnostic (or triage) test for use in remote, low-resource settings and for more simple and rapid tests for accurate detection of resistance to second-line anti-TB drugs.

131 New Medications, Innovative Approaches: Accelerate the TB Regimen Development Pipeline

Michael Hoelscher

University of Munich, Munich, Germany

This is an exciting time for tuberculosis drug development with a number of clinical trials reporting (REFAQUIN, OFLOTUB, REMoxTB). The challenge facing drug development is illustrated by the flouroquinolones trials to prove the promising results in Phase 2 regimens. It is time that we review drug development methodologies critically. The dizzying number of potential dosages and combinations of novel, established and repurposed agents requires rapid pre-selection of the most promising regimens from pre-clinical and early phase clinical trials. These regimens must be optimized at low cost to select the right regimen for a pivotal registration trial. A combination of innovative animal models, early clinical trial designs that gathers safety and DDI data as early as possible and efficacy outcome measurements in phase II studies that do not only look for bacillary clearance from sputum but also for relapse is needed. This presentation will review the different approaches that are currently under consideration.

132 Tuberculosis in Pregnancy

Amita Gupta

Johns Hopkins University School of Medicine, Baltimore, MD, US

Tuberculosis (TB) is a major cause of morbidity and mortality in women of childbearing age (15 to 44 years), accounting for almost 400,000 deaths in this age group every year. Pregnancy and HIV co-infection increase the likelihood that women with latent TB infection (LTBI) will progress to active TB disease, which raises the risk of poor maternal and infant outcomes. International guidelines

differ on the optimal regimen and dosing for TB treatment during pregnancy and postpartum in part because safety, tolerability, and pharmacokinetic (PK) data for many TB drugs are lacking in pregnant and postpartum women. This knowledge gap is of particular concern for women being treated for both TB and HIV infection and disease, who face overlapping drug toxicities and drug interactions between

TB and antiretroviral drugs. Promising new TB drugs have recently entered clinical development or have already been approved for use in non-pregnant adults, but currently there are no planned trials for any of these new agents in pregnant women. In this talk, I will highlight the management of TB during pregnancy including 1) the current knowledge and gaps regarding use of current and new antimycobacterial drugs during pregnancy as well as how pregnancy impacts the pharmacokinetics of anti-TB drugs and antiretroviral drugs; 2) how to manage antiretroviral therapy together with TB treatment during pregnancy; and 3) highlight new information about prevention of TB and unique aspects of treatment for latent TB infection that must be considered during pregnancy.

133 Tuberculosis in Children

Anneke C. Hesseling

Stellenbosch University, Cape Town, South Africa

This presentation will include an overview of the global epidemiology of tuberculosis in children, including the impact of HIV, and with specific emphasis on emerging data on drug-resistant TB.

Data will be presented on the historical challenges of evaluating existing and novel treatment strategies for TB in children. Emerging research opportunities and key early findings from pharmacokinetic studies and trials will be highlighted, addressing key pediatric populations including HIV-infected children, the treatment and prevention of MDR-TB, the use of novel drugs, and special treatment needs in infants and adolescents. An overview of research priories and planned and ongoing trials will be presented, and a framework to the evaluation of new TB drugs and regimens discussed.

Diagnostic challenges and new approaches to the diagnosis of TB, including novel biomarkers, molecular approaches and novel sampling strategies will be reviewed and global collaborative research efforts highlighted.

THURSDAY, FEBRUARY 26, 2015

Session PL-1 Plenary **4AB Auditorium**

8:30 am – 9:00 am

Cardiovascular Disease in HIV Patients: An Emerging Paradigm and Call to Action

134 Cardiovascular Disease in HIV Patients: An Emerging Paradigm and Call to Action

Steven Grinspoon

Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

Cardiovascular disease (CVD) has emerged as an important co-morbidity in HIV-infected patients. The relative risk of CVD, including myocardial infarction and stroke, is increased in HIV patients compared to age and gender-matched non HIV patients. Although some traditional risks, including smoking, are increased in HIV-infected patients and should be targeted for treatment, very often this disease occurs in relatively young, asymptomatic patients with only modest increases in traditional risk scores. Epidemiological studies suggest unique patterns of CVD in HIV patients, for example younger HIV-infected women may be less protected from CVD than younger women in the general population. Recent studies suggest an emerging mechanistic paradigm in which persistent immune activation and inflammation may contribute to atherosclerotic disease in HIV patients. In the HIV population, this disease manifests itself as subclinical, primarily non-calcified, vulnerable plaque, at increased risk for rupture. Indeed studies show increased rates of sudden cardiac death in the HIV population, consistent with acute rupture of vulnerable plaque. Monocyte activation and trafficking into the arterial surface may contribute to an inflammatory pro-thrombotic local milieu, more amenable to buildup of plaques with lipid laden foam cells and a thin necrotic surface. Indeed, molecular imaging techniques, assessing metabolic indices, suggest increased activity at the arterial surface among HIV patients, in association with immune activation and high risk, low attenuation, positively remodeled plaque. Treatment options to prevent CVD in HIV patients are critically needed. Emerging data suggests that targeting inflammation and immune activation may be useful to reduce CVD risk in the HIV population and specific strategies targeting these pathways are now under investigation. Significant evidence suggests that statins may offer

a number of benefits, potentially useful to lower CVD risk and prevent disease in the HIV population. Statins have been shown to reduce arterial inflammation, reduce monocyte activation and trafficking, and target key systemic inflammatory pathways. In addition, this class of agents reliably lowers LDL and thus may have advantages in reducing both traditional and nontraditional risk factors. Large scale NIH funded studies are now underway to test whether statins can safely prevent CVD in HV and the mechanisms by which this effect may occur.

Session PL-2 Plenary **4AB Auditorium**

9:00 am – 9:30 am

The Price of Selling Sex: HIV Among Female Sex Workers—The Context and the Public Health Response

135 The Price of Selling Sex: HIV Among Female Sex Workers—The Context and the Public Health Response

Frances M. Cowan

University College London, London, United Kingdom

Background: HIV prevalence among female sex workers (FSW) remains disproportionately high, on average 13 times higher than among the general population in low and middle income countries. FSW in sub-Saharan Africa are most severely affected. Effective HIV prevention interventions among FSWs include condom promotion, STI management, HIV testing and counselling, gender-based violence prevention, and community organising, but have not been taken to scale in many parts of the world. Structural and social factors further limit uptake of HIV prevention and care services. Mathematical modelling indicates that newer biomedical prevention technologies such as pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP) may provide additional prevention benefits over and above existing interventions, if mechanisms to support uptake, delivery and adherence can be developed and successfully implemented. Additionally, modelling suggests that PrEP is likely to be most cost-effective if used among those at highest risk of infection. Participation by FSW in the design and implementation of programs to ensure that they address local social and structural barriers to their health and rights has been shown to enhance program effectiveness. Modelling the impact of structural interventions suggests that decriminalisation of sex work would provide the greatest prevention gain across a range of settings through its combined effects on violence, police harassment, safer work environments, and HIV transmission pathways. Interventions to increase access to and retention in treatment and care services among FSW also need to be optimised, evaluated and taken to scale in a way that meets their needs. Achieving UNAIDS goal of 90:90:90 will not occur without sex worker led interventions that actively seek to address the social and structural barriers that FSW face when accessing HIV prevention and care services.

Conclusions: The presentation will i) describe the epidemiology of HIV among FSWs including the extent of, and the barriers to, their engagement in prevention and care, ii) present research on effective prevention interventions and the novel combination prevention and care approaches that are currently under evaluation iii) review recent modeling studies to look at the potential additive impact of adding these novel approaches.

Session O-11 Oral Abstracts **Room 6C**

10:00 am – 12:15 pm

Cardiovascular, Bone, and Kidney Health

136 Statin Therapy Reduces Coronary Noncalcified Plaque Volume in HIV Patients: A Randomized Controlled Trial

Janet Lo[1]; Michael Lu[2]; Ezinne Ihenachor[1]; Jeffrey Wei[1]; Sara Looby[1]; Kathleen Fitch[1]; Suhny Abbara[2]; Gregory Robbins[1]; Udo Hoffmann[2]; Steven Grinspoon[1]

[1]*Massachusetts General Hospital, Harvard Medical School, Boston, MA, US;* [2]*Massachusetts General Hospital, Boston, MA, US*

Background: Statins reduce cardiovascular events and deter progression of atherosclerosis. No studies have yet assessed the ability of statin treatment to achieve regression of coronary atherosclerosis in HIV-infected patients, a population demonstrated to have elevated risk of myocardial infarction.

Methods: In a randomized, double-blind, placebo-controlled trial, 40 HIV-infected participants with subclinical coronary atherosclerosis and low density lipoprotein (LDL)-cholesterol < 130mg/dL were randomized to one year of treatment with atorvastatin or placebo to determine the effect on coronary atherosclerotic plaque as assessed by coronary computed tomography angiography. We quantitatively assessed non-calcified plaque and high risk plaque features (low attenuation, spotty calcification, and positive remodeling index).

Results: After 12 months, atorvastatin reduced noncalcified coronary plaque volume compared to placebo (-19.4% [-39.2%, 9.3%] vs. +20.4% [-7.1%, 94.4%], p=0.009). In addition, the number of high risk plaques was significantly reduced by atorvastatin compared to placebo (change in number of low attenuation plaques -0.2 ± 0.8 vs. 0.4 ± 0.7 lesions, p=0.03 and change in number of positively remodeled plaques -0.2 ± 0.5 vs. 0.4 ± 0.9, p=0.04). Direct LDL-cholesterol (-38 ± 29 vs. 11 ± 21 mg/dL, p<0.0001) and lipoprotein-associated phospholipase A_2 (-52.2 ± 36.6 vs. -13.3 ± 42.8 ng/dL, p=0.005) significantly decreased with atorvastatin compared to placebo. Statin therapy was well-tolerated, with low incidence of clinical adverse events or laboratory abnormalities.

Conclusions: As compared to placebo**,** statin therapy reduces noncalcified plaque volume and high risk plaque features in HIV-infected patients with subclinical coronary atherosclerosis. Further studies should assess whether reduction in high risk coronary artery disease may translate into effective prevention of cardiovascular events in this at risk population of HIV patients.

137 Rosuvastatin Arrests Progression of Carotid Intima-Media Thickness in Treated HIV

Chris T. Longenecker[1]; Ying Jiang[1]; Sara M. Debanne[1]; Danielle Labbato[2]; Bruce Kinley[2]; Norma Storer[2]; **Grace A. McComsey**[1]

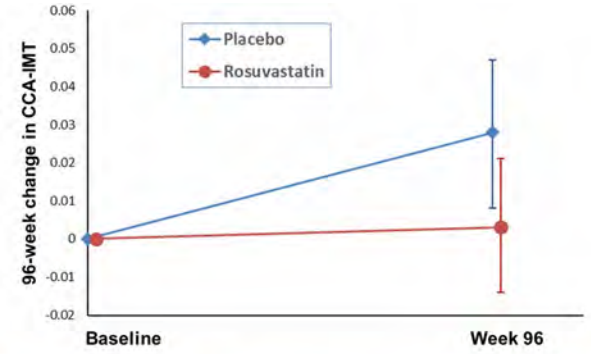
[1]*Case Western Reserve University, Cleveland, OH, US;* [2]*University Hospitals of Cleveland, Cleveland, OH, US*

Background: Statins slow progression of carotid intima-media thickness (IMT) and prevent cardiovascular events in HIV uninfected subjects. To what degree they may slow progression of carotid disease in HIV-infected patients on antiretroviral therapy (ART) is unknown.

Methods: SATURN-HIV was a 96-week double-blind, randomized clinical trial of 10 mg daily rosuvastatin versus placebo among 147 HIV-infected subjects on stable ART with LDL-cholesterol ≤130mg/dL and evidence of heightened T-cell activation (CD8+CD38+HLA-DR+ ≥19%) or increased inflammation (high sensitivity C-reactive protein ≥2mg/L). Randomization was stratified by protease inhibitor use and coronary artery calcium (CAC) score. Common carotid artery IMT (CCA-IMT) and presence of carotid plaque were assessed by ultrasound using semi-automated edge detection software. CAC was measured by gated cardiac CT. The study was designed to have >80% power to detect a 0.118 mm difference in the primary outcome of mean-mean CCA-IMT change. All analyses were intent to treat.

Results: Median (Q1, Q3) age was 46 (40, 53) years; 78% were male and 68% African American; 49% were on a protease inhibitor. Baseline median CCA-IMT was similar between groups [0.664 (0.624, 0.772) vs. 0.670 (0.602, 0.752) mm, statin vs. placebo, p=0.50]. At baseline, at least a third had carotid plaque (33% vs. 43%, statin vs. placebo, p=0.24) or detectable CAC (33% vs. 40%, statin vs. placebo, p=0.40). Overall, CCA-IMT progression was slower than anticipated [mean (standard deviation) 96 week change +0.015 (0.071) mm]. Within the placebo group, mean CCA-IMT progressed significantly over 96 weeks, but was unchanged in the statin group (see Figure). Mean difference in annualized rate of CCA-IMT

change between groups was 0.014 mm/yr. Among those without carotid plaque at baseline, there was no difference in development of new plaque by week 96 (4.9% vs. 6.5%, statin vs. placebo, p=0.82). Among those without CAC at baseline, there was a trend towards more detectable CAC after 96 weeks of statin (15% vs. 6%, statin vs. placebo, p=0.19).



	Mean 96 week change	95% Confidence Interval	Within group p-value	Between group p-value
Placebo	+0.028 mm	0.008 – 0.047	0.006	0.074
Rosuvastatin	+0.003mm	-0.014 – 0.021	0.714	

Change in mean-mean common carotid artery intima-media thickness (CCA-IMT) over 96 weeks according to study group assignment.

Conclusions: Rosuvastatin 10 mg daily appears to halt progression of carotid IMT in HIV-infected patients on ART with low LDL-cholesterol and high levels of immune activation. The effect on IMT progression is similar in magnitude to studies of HIV-uninfected populations and provides further justification for clinical outcomes trials in this population.

138 Calcified Plaque Burden Is Associated With Serum Gut Microbiota-Generated TMA in HIV

Suman Srinivasa[1]; Kathleen V. Fitch[1]; Janet Lo[1]; Hanane Kadar[2]; Kimberly Wong[1]; Suhny Abbara[3]; Dominique Gauguier[2]; Jacqueline Capeau[2]; Franck Boccara[2]; Steven K. Grinspoon[1]
[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]University Pierre & Marie Curie, Paris, France; [3]University of Texas Southwestern Medical Center, Dallas, TX, US

Background: Some gut microbiota-generated metabolites of phosphatidylcholine are recognized to be pro-atherogenic. The HIV population is more vulnerable to cardiovascular disease (CVD) than the general population and can develop impaired intestinal wall integrity and dysbiosis associated with inflammation. We investigated the novel relationship between microbiota-derived choline-related metabolites and coronary atherosclerosis in HIV.

Methods: 155 HIV-infected and 67 non-HIV-infected subjects without known CVD were previously recruited in a prospective study to assess coronary plaque by cardiac CT angiography. In the current study, we evaluated serum choline, trimethylamine (TMA) and trimethylamine N-oxide (TMAO) in association with plaque features and systemic inflammatory markers. A mass spectrometry-based method was designed to assay choline-related metabolites from serum. Linear regression was performed by Pearson's correlation after non-normally distributed variables were log transformed.

Results: Young, asymptomatic HIV-infected subjects(mean age 47±7 yrs, duration HIV 14±6 yrs, duration ART 8±5 yrs, CD4$^+$ count 552± 290 cells/μl, undetectable VL 86%) demonstrated significantly higher prevalence of plaque(53 vs. 35%, P=0.01) and total plaque segments(1.8±2.5 vs. 1.2±2.2, P=0.03) when compared to well-matched non-infected subjects with similar co-morbidities. TMA was significantly associated with number of total(r=0.20, P=0.02) and calcified(r=0.18, P=0.03) plaque segments; calcium score(r=0.22, P=0.006); calcium plaque volume (r=0.19, P=0.02) and mass(r=0.22, P=0.009); and lipopolysaccharides (LPS) (r=0.19, P=0.03) in the HIV cohort only. In multivariate modeling among HIV-infected subjects, TMA remained significantly associated with number of total(P=0.005) and calcified(P=0.02) plaque segments; calcium score(P=0.008); and calcium plaque volume(P=0.01) and mass(P=0.007), independent of Framingham Risk Score (FRS). Furthermore, TMA was still an independent predictor of total plaque segments(P=0.03), calcium score(P=0.04), and calcium plaque mass(P=0.03), after controlling for FRS and LPS. In contrast, there was no association of TMAO to plaque features in either cohort.

Conclusions: TMA, a microbiota-derived precursor of TMAO, may be a non-traditional cardiovascular risk factor which has independent effects on the number of coronary plaque segments and severity of calcified plaque burden in HIV. This relationship may derive from altered gut flora or microbial translocation unique to HIV.

139 Varenicline vs Placebo for Smoking Cessation: ANRS 144 Inter-ACTIV Randomized Trial

Patrick Mercie[3]; Caroline Roussillon[1]; Christine Katlama[4]; Aurélie Beuscart[1]; Samuel Ferret[2]; Nathalie Wirth[5]; David Zucman[6]; Xavier Duval[7]; Genevieve Chene[1]
ANRS 144 inter-ACTIV study group
[1]Inserm U897, Bordeaux, France; [2]Hosp. Saint-Louis, Paris, France; [3]Hosp. Saint-André, Bordeaux, France; [4]Hosp. La Pitié-Salpêtrière, Paris, France; [5]Hosp. De Brabois, Vandoeuvre les Nancy, France; [6]Hosp. Foch, Suresnes, France; [7]CIC 1425, Paris, France

Background: About half of HIV-infected patients are regular tobacco smokers in Europe, a higher prevalence than the general population. Tobacco is an important determinant of non AIDS morbidity and mortality (including vascular diseases and malignancies), a major reason to promote tobacco cessation. It is unclear whether varenicline is safe and efficacious for smoking cessation in HIV-infected patients. We evaluated varenicline at 48 weeks in regular smokers motivated to quit smoking.

Methods: Randomized (1:1), placebo-controlled clinical trial with a 12-week treatment period (from 0.5 mg once daily to 1 mg twice daily at the end of the first week) and a further 36-week follow-up, including smoking cessation counseling in both arms, conducted in 30 ANRS centers from Oct. 2009 to Jan. 2014. Self-reported tobacco abstinence was confirmed by exhaled carbon monoxide measurements at 9 weeks and at intervals up to 48 weeks. The primary endpoint was continuous abstinence rate from week 9 to 48. Secondary endpoints included continuous abstinence rate from week 9 to 12 and adverse events.

Results: 248 smokers were randomized; 213 included in the modified intention-to-treat analysis (102 varenicline, 111 placebo), others did not start trial treatment. Median age was 45 years, 83% male, median nadir CD4+ 213/mm^3, baseline CD4+ 617/mm^3 and undetectable HIV RNA 73%. Varenicline was associated with a higher continuous abstinence rate at 48 weeks than placebo: 17.6% *vs* 7.2% (*p=0.02)* and 34.3% *vs* 12.6% at 12 weeks (*p=0.0002)*. At 48 weeks, median CD4+ was 615/mm^3 and 80% had undetectable HIV RNA, without difference between arms. Grade 3/4 drug-related effects were reported in 7 patients in each arm, including 9 psychiatric side effects (5 in the varenicline arm *vs* 4 in

the placebo arm) and 3 gastrointestinal side effects (1 and 2, respectively). At least one depressive episode related to trial treatment was reported in 1 and 7 patients, respectively. Among 7 grade 3/4 cardiovascular events, 4 occurred in the varenicline arm (not treatment related) and 3 in the placebo arm. No neurovascular event was reported.

Conclusions: Varenicline is safe and effective in HIV infected patients with a 34% rate of tobacco abstinence at 12 weeks (end of treatment) and 18% at 48 weeks. These results are in the range of those reported in the HIV uninfected population. Varenicline should be considered as part of the standard of care in HIV-infected patients motivated to quit smoking.

140 Body Composition Changes After Initiation of Raltegravir or Protease Inhibitors

Grace A. McComsey[1]; Carlee Moser[2]; Judith S. Currier[8]; Heather Ribaudo[2]; Pawel Paczuski[2]; Michael P. Dube[5]; Robert L. Murphy[6]; Jennifer Rothenberg[7]; James H. Stein[4]; Todd T. Brown[3]

[1]Case Western Reserve University, Cleveland, OH, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]University of Wisconsin School of Medicine and Public Health, Madison, WI, US; [5]University of Southern California, Los Angeles, CA, US; [6]Northwestern University, Chicago, IL, US; [7]Social & Scientific Systems, Inc., Silver Spring, MD, US; [8]University of California Los Angeles, Los Angeles, CA, US

Background: Although lipoatrophy is uncommon with current antiretroviral therapy (ART), fat accumulation continues to occur, and its association with protease inhibitors (PIs) has been questioned. The effect of integrase inhibitors vs. PIs on body composition has not been established.

Methods: We compared the percentage change in lean mass (by DXA), peripheral fat (limb fat by DXA and subcutaneous abdominal fat (SAT) by CT scan of abdomen), and central fat (trunk fat by DXA and visceral abdominal fat (VAT) by CT) over 96 weeks in HIV-infected treatment-naive participants randomized to open labeled tenofovir disoproxil fumarate-emtricitabine (TDF/FTC) plus atazanavir-ritonavir (ATV/r), darunavir-ritonavir (DRV/r), or raltegravir (RAL) in ACTG 5260s, a substudy of A5257. DXA and CT measurements were standardized and centrally read. Linear regression, adjusting for the stratification factors of baseline cardiometabolic risk and HIV-1 RNA, was used to compare the 96-week percentage change in fat and lean mass in the two PI arms (ATV/r vs DRV/r) and, if not different, the PI arms were combined and compared to RAL arm. Associations between baseline biomarkers and changes in body composition were assessed with linear regression models adjusting for baseline age, BMI, HIV-RNA, CD4 count, sex and race/ethnicity. Within arm changes were assessed with signed-rank tests. All analyses were intent-to-treat.

Results: 328 participants were randomized; 90% were male and 44% white, non-Hispanic; median age was 36 years, HIV-1 RNA load 4.55 log10 copies/mL, and CD4 count 349 cells/μL. At week 96, the median percentage increases in limb fat, SAT, VAT, trunk fat, and lean mass were statistically significant in all arms (8.2%, 10.9%, 13.9%, 11.4%, 1.3%; $p<0.001$). Changes for all fat outcomes were not different between the PI arms ($p\geq0.36$), however greater gains in lean mass with ATV/r vs. DRV/r were detected (3.8% vs. 2.3%; $p=0.05$). There were no significant differences between the RAL arm and combined PI arm in any fat or lean mass endpoints ($p\geq0.36$). While lower baseline leptin and higher RNA levels were associated with greater gains in peripheral and central fat, higher baseline IL-6 was only associated with greater gains in peripheral fat.

Conclusions: In ART-naïve subjects initiating ART with TDF/FTC, RAL led to similar increases in lean mass, and central and peripheral fat as compared to ATV/r and DRV/r. We saw no evidence to suggest that the PIs were associated with greater increases in central fat than RAL

141 Fracture Prediction With Modified FRAX in Older HIV+ and HIV- Men

Michael T. Yin[1]; Melissa Skanderson[7]; Stephanie Shiau[1]; Katherine Harwood[1]; Josh Aschheim[3]; David Rimland[2]; Cynthia Gibert[5]; Maria Rodriguez-Barradas[4]; Roger Bedimo[6]; Julie Womack[7]

[1]Columbia University Medical Center, New York, NY, US; [2]VAMC and Emory School of Medicine, Atlanta, GA, US; [3]Arcadia Healthcare Solutions, New York, NY, US; [4]Baylor College of Medicine, Houston, TX, US; [5]VA Medical Center, George Washington University, Washington, DC, US; [6]University of Texas, Dallas, TX, US; [7]VA Connecticut Healthcare System, West Haven, CT, US

Background: Fracture rates are increased in HIV+ individuals. FRAX is a web-based fracture risk calculator used with or without bone mineral density (BMD) that estimates absolute 10-year risk of major osteoporotic (hip, spine, forearm, shoulder) and hip fracture. It is widely used for decision making in screening and treatment for fracture prevention. Since FRAX may underestimate fracture risk in HIV+ individuals; some experts recommend adding 'secondary osteoporosis' as a surrogate for HIV infection when using FRAX in an HIV+ patient.

Methods: From the Veterans Aging Study Virtual Cohort (VACS-VC), 26,037 HIV+/HIV- 50-70 year-old men were selected for whom complete data were available in 2000 to approximate all but 2 factors for FRAX calculation without BMD (history of secondary osteoporosis and parental hip fracture). Sum of estimated rates by this modified FRAX calculation was compared to observed 10-year fracture rates at similar body sites. Calibration (agreement between observed outcomes and predictions) by observed to estimated ratios (O/E) and discrimination (ability to discriminate subjects with and without outcome) by area under the curve (AUC) were compared by HIV status

Results: In 2000, HIV+ men were similar in age (56±5 vs 56±5, $p=0.11$) to HIV- men, but had lower weight (79±15 vs 89±16 kg, $p<0.01$), were more likely to report previous fracture, alcohol and glucocorticoid use, and less likely to smoke or have rheumatoid arthritis. More fractures occurred in HIV+ than HIV- men at major osteoporosis sites (4.61 vs 3.50%, $p<0.01$) and hip (1.32 vs 0.85%, $p<0.01$). Estimated rates by the modified FRAX were also higher for HIV+ than HIV- men at major osteoporosis sites (2.85 ±1.5 vs 2.71±1.4%, $p<0.01$) and hip (0.29 ±0.4 vs 0.24±0.3%, $p<0.01$). Calibration for major osteoporotic fracture was worse in HIV+ than HIV- men (1.62 vs 1.29, $p=0.028$). Discrimination for modified FRAX was poor, but did not differ by HIV status (Table). Adding 'secondary osteoporosis' as a surrogate for HIV-infection risk in FRAX calculation improved calibration to level of HIV- men (O/E=1.20), but did not improve discrimination (AUC=0.600).

		Major osteoporitic fractures		Calibration		Discrimination	
	N	Observed	Expected	O/E	95% CI	AUC	95% CI
All	24451	935	673	1.39	1.30, 1.48	0.58	0.57, 0.60
HIV+	7064	326	201	1.62	1.45, 1.81	0.60	0.57, 0.63
HIV-	17387	609	471	1.29	1.19, 1.40	0.57	0.55, 0.60

Conclusions: In this study of older men, the modified FRAX score underestimates fracture rates more in HIV+ than HIV- men, and does not discriminate well between those at risk and not at risk for future fracture. Including 'secondary osteoporosis' as a surrogate risk factor may improve the performance of the modified FRAX in HIV+ patients.

142 Exposure to Antiretrovirals (ARVs) and Development of Chronic Kidney Disease (CKD)

Amanda Mocroft[1]; Jens D. Lundgren[2]; Michael Ross[3]; Christoph Fux[4]; Peter Reiss[5]; Olivier Moranne[6]; Philippe Morlat[7]; Antonella d'Arminio Monforte[8]; Ole Kirk[2]; Lene Ryom[2]
On behalf of the The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group

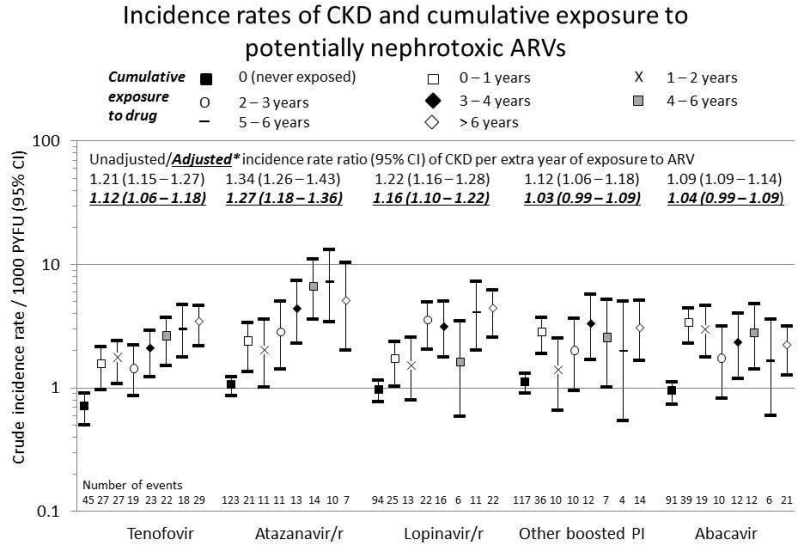
[1]University College London, London, United Kingdom; [2]Copenhagen HIV Programme, Centre for Health and Infectious Diseases Network, University of Copenhagen, Denmark, Denmark; [3]Division of Nephrology, Mount Sinai School of Medicine, New York, NY, US; [4]Clinic for Infectious Diseases and Hospital Hygiene, Kantonsspital Aarau, Aarau, Switzerland; [5]Academic Medical Center, Div. of Infectious Diseases and Dept. of Global Health, University of Amsterdam, Amsterdam, Netherlands; [6]Université de Bordeaux, Inserm U 897, Bordeaux, France; [7]Public Health Department, Nice, France; [8]Istituto Di Clinica Malattie Infettive e Tropicale, Milan, Italy

Background: Previous studies in persons with an initially normal eGFR have been underpowered to assess whether the incidence of CKD increases immediately after starting potentially nephrotoxic ARVs and then remains stable or continues to increase with duration of exposure.

Methods: D:A:D study participants were followed from baseline until earliest of CKD, last eGFR, 1/1/2013 or last visit plus 6 months. Baseline was defined as the first eGFR after 1/1/2004; persons with <2 eGFRs after baseline or where baseline eGFR <90 ml/min/1.73m^2 were excluded. CKD was defined as confirmed (>3 months apart) eGFR <60 ml/min/1.73m^2

and chronic renal impairment (CRI) as confirmed (>3 months apart) eGFR <70 ml/min/1.73m^2. Poisson regression was used to estimate the incidence of CKD associated with cumulative exposure to or time since stopping tenofovir (TDF),ritonavir-boosted atazanavir (ATV/r), lopinavir (LPV/r), other ritonavir-boosted protease inhibitors (BPI) or abacavir (ABC).

Results: 23560 persons were included with median baseline eGFR 110ml/min/1.73m^2 (IQR 100–125), age 39 years (IQR 33–45) and CD4 440/mm^3 (IQR 293–629). During a median follow-up of 6.3 years (IQR 4.4–8.0), 210 persons developed CKD (0.9%; incidence 1.48/1000 PYFU; 95% CI 1.28–1.68). The crude incidence of CKD increased as exposure to TDF, LPV/r and ATV/r increased, but not as clearly for BPI and ABC (Figure). After adjustment, there was a significant increase in CKD associated with increasing exposure to TDF, ATV/r and LPV/r (all p<0.0001) but not other BPI (p=0.44) or ABC (p=0.12; Figure). Results were consistent for CRI and when limited to those currently on ARVs. There was a decrease in the incidence of CKD as time since stopping TDF increased, with no clear picture for the other ARVs. Those who had stopped TDF for >2 years had a significantly raised incidence of CKD (adjusted incidence rate ratio 2.47; 95% CI 1.36–4.48) compared to those never exposed to TDF.



Multivariate models adjusted for race, HIV exposure risk, D:A:D cohort, study, gender, nadir CD4, baseline date and eGFR, and hepatitis B*, hepatitis C*, smoking status*, BMI*, family history of CVD*, viral load*, CD4*, a new AIDS diagnosis within the past 12 months* (time updated variables*). Models were additionally adjusted for cumulative exposure to indinavir.

Conclusions: The association between TDF, ATV/r, LPV/r and CKD in persons with an initially normal eGFR was not limited to an increased incidence immediately after starting the ARV, but clearly persisted with increasing exposure to TDF, LPV/r and ATV/r. After 6 years exposure, the relative risk of CKD was increased by 97%, 320% and 140% for TDF, ATV/r and LPV/r respectively. A clear decrease in the incidence of CKD after stopping ARVs was only observed for TDF; but the incidence remained significantly higher 2 years after stopping compared to those who had never started TDF.

143LB Renal and Bone Safety of Tenofovir Alafenamide vs Tenofovir Disoproxil Fumarate

Paul E. Sax[7]; Michael S. Saag[2]; Michael T. Yin[3]; Frank A. Post[4]; Shinichi Oka[8]; Ellen Koenig[5]; Benoit Trottier[9]; Jaime Andrade-Villanueva[6]; Huyen Cao[1]; Marshall W. Fordyce[1]

[1]Gilead Sciences Inc, Foster City, CA, US; [2]University of Alabama at Birmingham, Birmingham, AL, US; [3]College of Physicians and Surgeons, Columbia University, New York, NY, US; [4]King's College Hospital, London, United Kingdom; [5]Dominican Institute for Virologic Studies, Santo Domingo, Dominican Republic; [6]Unidad de VIH del Hospital Civil de Guadalajara, Guadalajara, Mexico; [7]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, US; [8]National Center for Global Health and Medicine, Japan, Tokyo, Japan; [9]Clinique Medicale l'Actuel, Montreal, Canada

Background: Off-target renal and bone side effects may occur with tenofovir disoproxil fumarate (TDF) use. Compared with TDF, tenofovir alafenamide (TAF) results in significantly reduced plasma tenofovir (TFV) and may have less renal and bone toxicity.

Methods: Treatment naïve HIV-1$^+$ adults were randomized 1:1 to a single tablet regimen of E/C/F/TAF or E/C/F/TDF once daily in two double blind studies. Assessments included measures of renal function and bone mineral density (BMD). Four pre-specified secondary safety endpoints were tested: serum creatinine, treatment-emergent proteinuria, spine and hip BMD. Week 48 off-target side effects data are described.

Results: Combined, the two studies randomized and treated 1,733 subjects. Plasma TFV was >90% lower (mean [%CV] AUC_{tau} 297 (20) vs. 3,410 (25) nghr/mL) in the E/C/F/TAF arm, compared to the E/C/F/TDF arm. Serum creatinine (mean [SD] change: +0.08 [0.124] vs +0.11 [0.217] mg/dL, p<0.001), quantified proteinuria (UPCR, median [Q1, Q3] % change; -3 [-35, +43] vs +20 [-23, +76], p<0.001), albuminuria (UACR, median [Q1, Q3] % change; -5 [-33, +36] vs +7 [-27, +62], p=0.001), retinol binding protein (RBP:Cr, median [Q1, Q3] % change; +9 [-23, +49] vs +51 [+3, +133]), beta-2-microglobulin (β-2-Mg:Cr, median [Q1, Q3] % change; -32 [-57, +4] vs +24 [-34, +168]), and fractional excretion of phosphate (median [Q1, Q3] % change; +0.9 [-2.0, +4.5] vs +1.7 [-1.6, +5.3]), all favored E/C/F/TAF. There were no cases of proximal tubulopathy in either arm. Mean (SD) % decrease in BMD was significantly less in the E/C/F/TAF arm for both lumbar spine (-1.30 [3.08] vs -2.86 [3.25], p<0.001) and total hip (-0.66 [3.26] vs -2.95 [3.41], p<0.001). Increases from baseline in bone turnover biomarkers (C-telopeptide and P1NP) and parathyroid hormone were significantly smaller in the E/C/F/TAF group compared with the E/C/F/TDF arm (p < 0.001 for all). Increases in fasting lipid parameters (total cholesterol, HDL, direct LDL, and triglycerides) were greater in the E/C/F/TAF arm (p < 0.001 for all).

Conclusions: Through 48 weeks, subjects receiving E/C/F/TAF had significantly better outcomes related to renal and bone health than those treated with E/C/F/TDF; lipid outcomes favored E/C/F/TDF. Collectively these data demonstrate important safety benefits of TAF relative to TDF, especially given the aging of the HIV population and the need for long-term treatment.

144 Special Presentation: Update on National Heart, Lung, and Blood Institute High-Impact AIDS Research

Monica Shah

National Heart, Lung, and Blood Institute, Bethesda, MD, US

Session O-12 Oral Abstracts
Room 6AB

10:00 am – 12:00 pm

Curing HCV: Mission Accomplished

145 The Burden of Liver Disease Among Persons With Hepatitis C in the United States

Monina Klevens[1]; Xiaohua Huang[2]; Anthony E. Yeo[2]; Mouneer Odeh[2]; Rick L. Pesano[2]; John W. Ward[1]

[1]US Centers for Disease Control and Prevention, Atlanta, GA, US; [2]Quest Diagnostics, Madison, NJ, US

Background: In the United States, the CDC recommends one-time hepatitis C virus (HCV) antibody testing for persons born from 1945-1965 due to the higher seroprevalence of HCV infection in this group. However, the burden of liver disease among the infected population has not been described.

Methods: Data were from Quest Diagnostics, a CDC partner, which conducts routine HCV tests in all states. For this analysis, all test data were anonymized and de-duplicated at the person level. The sample included all tests for which a first positive HCV RNA result was known for a given year from 2010-2013. Values for AST, platelet count and ALT, were combined with age to calculate FIB-4, a non-invasive scoring system indicative of liver fibrosis. Test data were then examined by year and stage of fibrosis.

Results: During 2010-2013, a total of 273,143 persons had a first positive HCV-RNA test result and known date of birth. Of these, 186,416 (68.2%) were born from 1945-1965. For all years combined, most persons in the birth cohort had moderate fibrosis (42.3%) followed by severe fibrosis (28.7%) and cirrhosis (22.7%). Almost no variation was found over the four-year period by stage of FIB-4 (Table). In 2013, 53.1% of persons born from 1945-1965 had severe fibrosis or cirrhosis; this was higher than among persons born after 1965 (12.4%) but lower than among persons born before 1945 (79.7%).

Number and percent+ of persons born during 1945-1965 with a first positive HCV-RNA test result* by year and stage of fibrosis

Category of fibrosis (mean FIB-4)	2010	2011	2012	2013
No fibrosis (<1.0)	2712 (10%)	2366 (10%)	1625 (9%)	1209 (9%)
Moderate fibrosis (1.0-2.0)	11195 (41%)	10369 (42%)	7460 (40%)	5566 (40%)
Severe (2.0-3.7)	7378 (27%)	6750 (27%)	5310 (28%)	3982 (28%)
Cirrhosis (≥3.8)	5908 (22%)	5140 (21%)	4266 (23%)	3220 (23%)
Total including missing/unknown^	38471	35458	27315	20687

+ Percentage excluding unknown/missing

*Not known to have a previous positive RNA test

^ Includes persons with ≥1 parameter missing

Conclusions: Alarmingly, about one-half of HCV-infected persons born from 1945-1965 had severe fibrosis or cirrhosis as evidenced by FIB-4 scoring. No decreases were observed in this proportion over time. Persons with this stage of severe HCV-related liver disease are a high priority for treatment. Improved birth cohort screening for HCV and linkage to recommended care and treatment are urgently needed to prevent complications.

146 High Efficacy of Daclatasvir/Asunaprevir/PR in HIV/HCV1-4 Null Responders (ANRS HC30)

Lionel Piroth[1]; Hubert Paniez[2]; Corine Vincent[2]; Karine Lacombe[3]; David Rey[4]; Didier Neau[5]; Jacques Izopet[6]; Alpha Diallo[7]; Laurence Meyer[2]; Jean-Michel Molina[8]

[1]CHU Dijon, Dijon, France; [2]Inserm, Paris, France; [3]Hôpital Saint-Antoine, Paris, France; [4]Strasbourg University Hospital, Strasbourg, France; [5]CHU, Bordeaux, France; [6]CHU, Toulouse, France; [7]Inserm-ANRS, Paris, France; [8]CHU Saint Louis, Paris, France

Background: Few direct anti-HCV agents (DAAs) have been studied in difficult to treat HIV co-infected patients, in particular null responder and cirrhotic. Daclatasvir and Asunaprevir combined with pegylated interferon-ribavirin (PR) have shown promising results in HCV mono-infected patients.

Methods: An open label, single arm, phase 2 study (ANRS HC30 QUADRIH) in HIV/HCV genotype (GT) 1 or 4 co-infected patients, null responders to prior pegylated interferon-ribavirin (PR) standard bitherapy. Patients had to have plasma HIV RNA levels < 400 cp/ml and received a 4-week lead-in phase with PR, followed by 24 weeks of asunaprevir (100mg bid), daclatasvir (60 mg qd), and PR. The primary endpoint was sustained virological response 12 weeks after the end of treatment (SVR12) using ITT analysis.

Results: Seventy-five patients (59 men/16 women) were included, median age 50 (IQR: 48 - 53) years, 27 (36%) cirrhotic. All were on a raltegravir-based regimen, 92% with baseline (BL) plasma HIV RNA level <50cp/ml, with BL median CD4 count 748 (481 - 930)/mm^3. BL plasma HCV viral load was 6.1 (5.8 - 6.6) log10 UI/mL.

The global SVR12 rate was 96.0% (72/75; 95%CI: 91.6%-100%). SVR12 was 92.6% (25/27; 82.7%-100%) in cirrhotic patients, 94.6% (35/37; 87.3%-100%) in GT1and 97.4% (37/38; 92.3%-100%) in GT 4. Eleven patients (15%) reached HCV undetectability at W5, 28 (37%) at W6, and 45 (60%) at W8. In the 51 patients experiencing less than a 1 $\log_{10}$ IU/ml HCV RNA decrease during the lead-in phase, SVR12 was 94.1%.

Six patients (8%) prematurely stopped HCV therapy, 2 due to virological breakthrough, and 4 to adverse events (one lung cancer, 3 infections). One of these patients (with BL platelets<150,000/mm^3 and BL albumin<35g/l) died from multivisceral failure. Overall, 35 serious adverse events occurred in 21 (28%) patients (9 cirrhotic and 12 non cirrhotic, p=0. 44), including hematological (15%, mainly anemia and neutropenia), gastrointestinal (5%), psychiatric events (5%, mainly insomnia), and infections (5%).

Conclusions: In HIV/HCV GT1/4 null responders, one third of whom had cirrhosis, a 24-week regimen combining daclatasvir/asunaprevir/PR was associated with a very high SVR12 rate. The safety profile was acceptable, even though cirrhotic patients with low albumin and platelets levels should be closely monitored This combination represents a new treatment option in this highly difficult to treat population.

147 High SVR Regardless of Time to Suppression With ABT-450/r/Ombitasvir & Dasabuvir+RBV

David Wyles[1]; Joseph J. Eron[2]; Roger Trinh[3]; Jay Lalezari[4]; Chia Wang[5]; Laveeza Bhatti[6]; Peter Gulick[7]; Barbara McGovern[3]; Linda Fredrick[3]; Mark Sulkowski[8]

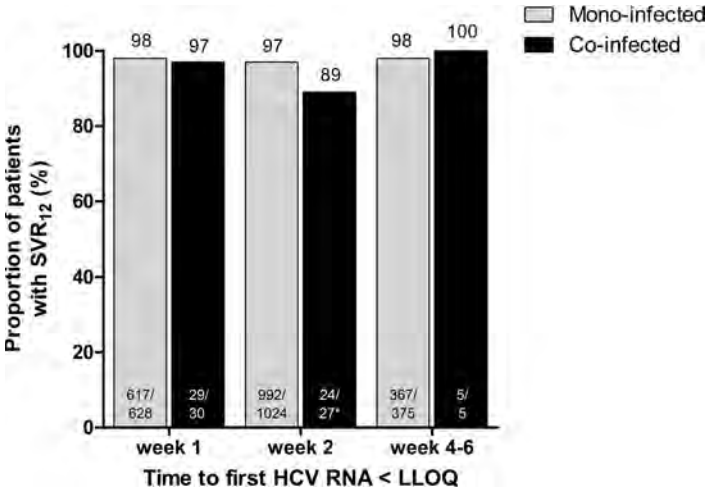
[1]University of California San Diego, La Jolla, CA, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]Abbvie Inc, North Chicago, IL, US; [4]Quest Clinical Research, San Francisco, CA, US; [5]Virginia Mason Medical Center, Seattle, WA, US; [6]AIDS Healthcare Foundation, Los Angeles, CA, US; [7]Michigan State University, East Lansing, MI, US; [8]Johns Hopkins University, Baltimore, MD, US

Background: SVR12 rates >90% have been achieved with the interferon-free 3 direct-acting antiviral regimen (3D) of co-formulated ABT-450 (identified by AbbVie and Enanta)/ritonavir/ombitasvir with dasabuvir +/- RBV in HCV genotype (GT) 1 mono-infected patients. We assessed HCV RNA viral suppression over time in HCV/HIV-1 co-infected patients treated with 3D+RBV and in mono-infected patients treated with 3D+/-RBV.

Methods: Data from the pooled population of HCV GT-1 mono-infected patients from six phase 3 trials of 3D+/-RBV for 12 weeks or 24 weeks (N=2053) and the HCV/HIV-1 co-infected patients from the Phase 2 TURQUOISE-I trial of 3D+RBV for 12 or 24 weeks (N=63) were included. Patients who experienced non-virologic failure were excluded from the

efficacy analysis (N=26 mono-infected; N=1 co-infected). HCV RNA was determined using the Roche COBAS TaqMan RT-PCR assay; lower limit of quantification (LLOQ) =25 IU/ml. SVR_{12} rates were analyzed according to the first week HCV RNA ⟨LLOQ was attained.

Results: Mono- and co-infected patient groups were well matched for IL28B non-CC GT (78% [1607/2053] mono-infected; 81% [51/63] co-infected) and proportion with cirrhosis (19% [384/2053] mono-infected; 19% [12/63] co-infected). More co-infected than mono-infected patients were black (24% [15/63] vs 6% [123/2053], respectively). Most patients achieved HCV RNA ⟨LLOQ by week 2, regardless of mono- or co-infection (1652/2027 [81%] mono-infected, 57/62 [92%] co-infected); stratifying this by cirrhosis state yielded 283/374 (76%) for cirrhotic and 1369/1653 (83%) for non-cirrhotic mono-infected patients and 11/12 (92%) for cirrhotic and 46/50 (92%) for non-cirrhotic co-infected patients. By week 4, the 5 remaining co-infected patients who were not suppressed at week 2 had HCV RNA < LLOQ. Two out of three co-infected patients who achieved HCV RNA ⟨LLOQ at week 2 and did not achieve SVR_{12} had documented HCV re-infection. Similar to mono-infected patients, SVR_{12} rates (despite documented re-infection) in co-infected patients were high (89-100%), regardless of time of initial HCV viral suppression (Figure). The overall safety profile was similar for mono- and co-infected patients.



*Virologic failures occurring in 2 patients appear to have resulted from reinfection based on analyses of baseline and virologic failure samples

Conclusions: Both HCV mono- and HCV/HIV-1 co-infected patients achieved rapid HCV viral suppression with 3D+/-RBV treatment. SVR_{12} rates were high regardless of time of first virologic response.

148 The Paradox of Highly Effective Sofosbuvir Combo Therapy Despite Slow Viral Decline

Thi Huyen Tram Nguyen[1]; **Jérémie Guedj**[1]; Laetitia Canini[2]; Anu Osinusi[5]; Phillip S. Pang[5]; John McHutchison[5]; Henry Masur[6]; Anita Kohli[3]; Shyam Kottilil[4]; Alan S Perelson[2]

[1]IAME, UMR 1137, Inserm, F-75018 Paris, France; Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France, Paris, France; [2]Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, NM, US; [3]Clinical Research Directorate/Clinical Monitoring Research Program, Leidos Biomedical Research, Inc, Frederick National Laboratory for Cancer Research, Frederick, MD, US; [4]Laboratory of Immunoregulation, NIAID, NIH, Bethesda, MD, US; [5]Gilead Sciences, Inc, Foster City, MD, US; [6]NIH Clinical Center, Bethesda, MD, US

Background: The SYNERGY trial demonstrated that high cure rates for HCV infection could be achieved after 12 week treatment with sofosbuvir (SOF) and ledipasvir (LDV), and after only 6 weeks if GS-9669 (a non-nucleoside polymerase inhibitor) or GS-9451 (a protease inhibitor) was added *(Kohli et al., The Lancet 2014)*. Here we employed viral kinetic modeling to better understand the effect of each of these drugs in this very rapid and effective cure of HCV.

Methods: In order to evaluate the effect of each agent, we conducted a pooled analysis of the early viral kinetics in patients treated with SOF + ribavirin (RBV) (*Osinusi et al., JAMA 2013*), SOF + LDV and SOF+LDV+GS9669/GS9451. Viral kinetics were fitted using a multiscale model that allows one to distinguish the effect of each agent in blocking vRNA replication, ε_α, from blocking viral assembly/secretion, ε_s *(Guedj et al., PNAS 2013)*.

Results: The viral load decline was initially much more rapid in all arms of Synergy than in patients treated with SOF + RBV. This was attributed in our model to a high effectiveness of LDV in blocking viral assembly/secretion (ε_s=99.7%). In contrast, the delayed response in patients treated with SOF + RBV suggests that SOF has only a minimal effect in blocking assembly/secretion. However by day 3, patients treated with SOF + RBV achieved largely comparable levels of virus as the patients in all arms of Synergy (Fig 1), demonstrating a high effectiveness of SOF in blocking vRNA production (ε_α=99.96%). Surprisingly, the total effectiveness in blocking vRNA production was significantly lower in patients receiving SOF+LDV±GS-9669 (ε_α=96.5%, $P<10^{-10}$) and, to a lesser extent, SOF+RBV±GS-9451 (ε_α=98.5%, $P<10^{-10}$). Eventually, the final phase of viral decline was largely similar in all groups, and similar to that observed with IFN-based therapies.

Consistent with this slow final phase, the model predicted SVR rate of 85.2% after 24 weeks of SOF+RBV, but only 43% and 10% after 12 and 6 weeks of SOF+LDV and SOF+LDV+GS9669/GS9451, respectively, i.e., much lower than what was observed in the Synergy trial.

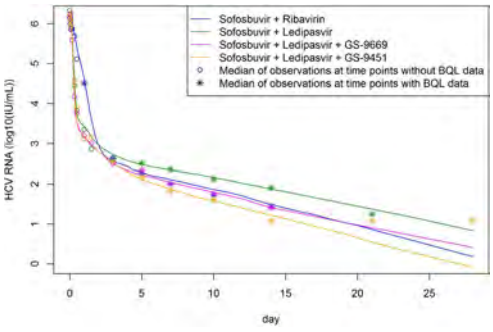


Figure 1: Median observed viral load and median predicted viral decay curves using the multiscale model for different treatment combinations of Synergy and Spare trials. BLQ=below limit of quantification

Conclusions: The kinetics of viral decline in patients of the Synergy trial was remarkably slow in regard of the very rapid cure of HCV. This suggests that HCV RNA is not a reliable marker for predicting outcome of treatment containing SOF+LDV. Additional mechanisms of action that are not reflected in the observed viral load, such as production of non-infectious virus, may explain the high cure rates.

149 Real-World Pharmaceutical Costs in the Simeprevir/Sofosbuvir Era: $164,485 per SVR4

Kian Bichoupan[1]; Neeta Tandon[2]; Rachana Yalamanchili[1]; Neal M. Patel[1]; Sweta Chekuri[1]; Alyson Harty[1]; Thomas Schiano[1]; Ponni V. Perumalswami[1]; Douglas Dieterich[1]; Andrea D. Branch[1]

[1]Mount Sinai School of Medicine, New York, NY, US; [2]Janssen Scientific Affairs, Titusville, NJ, US

Background: Pharmaceutical costs-per-sustained virologic response (SVR4) were determined for patients treated with simeprevir (SMV) and sofosbuvir (SOF) at a large metropolitan medical center.

Methods: The SVR4 rate was calculated for 103 genotype 1 HCV-infected patients who started on SMV- SOF-containing regimens between 12/2013-6/2014. Advanced fibrosis/cirrhosis was defined as a FIB-4 score ≥ 3.25. Costs were based on Red Book Wholesale Acquisition Costs and the number of days on treatment: SMV=$790/d, SOF =$1,000/d, and RBV=$8.58/d. The rate of relapse between 4 and 12 weeks after the end of treatment (EOT) was determined for 41 patients with the necessary follow up data. Episodes of hepatic decompensation and other serious adverse events (SAEs) were noted.

Results: The median age of the 103 patients was 60 years (interquartile range [IQR] = 54-65 years), 14% had HIV/HCV co-infection, 13% were black, 74% were male, 46% had a score ≥ 3.25; 74% had genotype 1a HCV, 25% were naïve to treatment, 28% previously failed therapy with an HCV protease inhibitor. Median baseline laboratory values were as follows: platelet count = 154 x103/μL (IQR: 111-194 x103/μL), albumin = 4.1 g/dL (IQR: 3.8-4.4 g/dL), total bilirubin = 0.7 mg/dL (IQR: 0.5 – 1.0 mg/dL), median log HCV viral load = 6.25 IU/mL (IQR: 5.90 – 6.72 IU/mL). The treatment completion rate for the entire group was 98%, see Table. Overall, 93 (90%) achieved SVR4: SMV/SOF/RBV 77/85 (91%), SMV/SOF 16/18 (89%). Three (2.9%) patients experienced hepatic decompensation/SAE. The SVR4 rates for mono-infected and HIV/HCV patients were 89% and 100% (p=0.35), respectively. The overall mean pharmaceutical cost-per-SVR4 was $164,485. Among 41 patients with the necessary follow up, three (7%) relapsed between week-4 and week-12 post EOT.

Regimen (duration of treatment)	N	FIB-4 ≧ 3.25	Previous protease inhibitor failure	Completed therapy	Serious adverse event or hepatic decompensation	SVR4 rate	Mean cost per SVR4
SOF/SMV/RBV (12 weeks)	85	43 (51%)	27 (32%)	84 (99%)	0 (0%)	77 (91%)	$165,142
SOF/SMV (12 weeks)	18	6 (33%)	2 (11%)	17 (94%)	3 (17%)	16 (89%)	$161,323
Total	103	2 (11%)	29 (28%)	101 (98%)	3 (2.9%)	93 (90%)	$164,485

Cost per SVR by Regimen

Conclusions: In the SMV/SOF era, 98% of patients completed the planned regimen in real world clinical practice. The SVR4 rate was 90% and the mean pharmaceutical cost-per-SVR4 was $164,485. Treatment was highly effective in patients with HIV/HCV co-infection. Rates of decompensation/SAE were < 3%. Surveillance beyond SVR4 is needed to determine the final SVR rate. Seven percent of patients with follow up data relapsed between 4 and 12 weeks EOT.

150 Impact of Deferring HCV Treatment on Liver-Related Events in HIV+ Patients

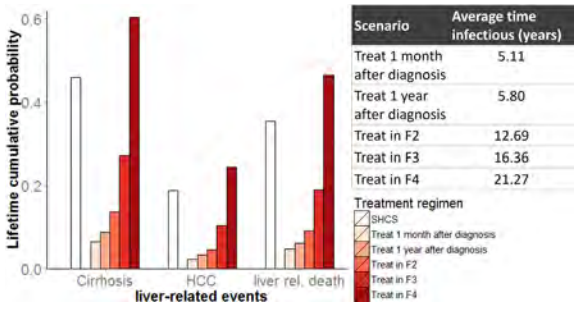
Cindy Zahnd[1]; Luisa P. Salazar-Vizcaya[1]; Jean-François Dufour[2]; Beat Müllhaupt[3]; Gilles Wandeler[1]; Roger Kouyos[3]; Barbara Bertisch[1]; Andri Rauch[2]; Olivia Keiser[1]
The Swiss HIV and Hepatitis C Cohort Studies

[1]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland; [2]University Hospital Bern, Bern, Switzerland; [3]University Hospital Zurich, Zurich, Switzerland

Background: Successful treatment of HCV infections substantially reduces the risk of liver-related complications. However, cost considerations and the availability of better treatment options in the future often leads to the deferral of treatment of HCV infection in patients with limited liver fibrosis. In this study, we modelled the impact of different treatment strategies on liver fibrosis progression among HIV-infected patients with incident HCV infection.

Methods: We developed an individual-based model of liver disease progression. We parameterized it with observed data on incident HCV infections among men who have sex with men from the Swiss HIV Cohort Study (SHCS) and with published data. We simulated patients from HCV infection through stages of liver disease: from fibrosis grade F0 to F4, decompensated cirrhosis, hepatocellular carcinoma and death. Liver disease progression was affected by age at HCV infection and alcohol consumption. Patients also progressed through the care cascade: they could be diagnosed, treated and succeed or fail treatment. We assumed treatment efficacy with Interferon (IFN)-free regimen was 90%. Successfully treated patients had a residual liver fibrosis progression of 0.1 times the rate of patients with detectable HCV. We compared liver-related events and duration of infectiousness (ie. detectable viral load) between the following strategies: treatment of all patients one month after diagnosis, one year after diagnosis or as they reach F2, F3 or F4.

Results: Delaying treatment until 1 year after diagnosis or until F2, F3 or F4 led to 14, 43, 142 and 418 additional cases of liver-related deaths per 1000 HCV infections as compared with treating all patients one month after diagnosis. The average time people were infectious increased from 5 years with early (one month after diagnosis) to 21 years with late (F4) treatment (*Figure*).



SHCS is our base scenario and is given here for reference, it depicts current practise in the SHCS.

HCC: Hepatocellular Carcinoma

Conclusions: Our model suggests that timely treatment of HCV infection is important: Patients can progress to end-stage liver disease after HCV clearance if treatment is delayed until later stages of liver disease due to imperfect treatment responses and residual fibrosis progression in HIV-infected patients. Delaying treatment also increases the risk of HCV transmission: the average time during which patients are infectious is four times higher if patients are treated in F4 than if they are treated one month after diagnosis.

151LB Daclatasvir in Combination With Sofosbuvir for HIV/HCV Coinfection: ALLY-2 Study

David Wyles[1]; Peter Ruane[2]; Mark Sulkowski[3]; Douglas Dieterich[4]; Anne Luetkemeyer[5]; Timothy Morgan[6]; Kenneth E. Sherman[7]; Zhaohui Liu[8]; Stephanie Noviello[8]; Peter Ackerman[8]

[1]University of California San Diego, La Jolla, CA, US; [2]Ruane Medical and Liver Health Institute, Los Angeles, CA, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]Icahn School of Medicine at Mount Sinai, New York, NY, US; [5]University of California and San Francisco General Hospital, San Francisco, CA, US; [6]VA Long Beach Healthcare System, Long Beach, CA, US; [7]University of Cincinnati College of Medicine, Cincinnati, OH, US; [8]Bristol-Myers Squibb Co, Princeton, NJ, US

Background: The pangenotypic, once-daily combination of daclatasvir (DCV) and sofosbuvir (SOF) achieves high rates of sustained virologic response (SVR) in patients with chronic HCV infection. DCV+SOF has favorable safety and drug-drug interaction profiles and a high barrier to resistance, supporting the phase 3 ALLY-2 study of DCV+SOF in patients with HIV/HCV coinfection.

Methods: This randomized, open-label study enrolled HCV treatment-naive (N=151) or experienced (N=52) adults coinfected with HIV and HCV (any genotype). Naive patients were randomly assigned (2:1), with stratification by cirrhosis status and HCV GT, to receive 12 or 8 weeks of once-daily SOF 400mg + DCV 60mg (dose-adjusted for concomitant antiretrovirals: 30mg with ritonavir-boosted PIs, 90mg with NNRTIs except rilpivirine). Experienced patients received this same regimen for 12 weeks. The primary endpoint was HCV RNA < LLOQ (25 IU/mL) at posttreatment Week 12 (SVR12) in naive GT1 patients treated for 12 weeks.

Results: Treatment arms were well balanced with a median age of 52 y, 87% male, and 62% white/34% black. 83%, 9%, 6%, and 2% of patients, respectively, had GT1, 2, 3, and 4 infection; median baseline HCV RNA was 6.7 log10 IU/mL; 14% had cirrhosis. The median baseline CD4 count was 565 cells/μL and 94% had HIV RNA <50 cp/mL. 99, 50, and 50 patients, respectively, received PI-based, NNRTI-based, or other (primarily INI-based) cART; 4 patients did not receive cART. 199/203 (98%) patients completed therapy; 2 patients discontinued early for noncompliance and 2 for incarceration. Overall, SVR12 was achieved by 97% and 98% of naive and experienced patients, respectively, after 12 weeks of therapy, and by 76% of naive patients after 8 weeks (Table). Among patients treated for 12 weeks, SVR12 rates were similar regardless of prior treatment experience, HCV GT or GT1 subtype, cirrhosis status, concurrent cART regimen, or race. There were no virologic breakthroughs; 2/153 patients (1%) in the 12-week group and 10/50 (20%) in the 8-week group had posttreatment relapse. There were no treatment-related serious AE or AE leading to discontinuation. Treatment-emergent grade 3/4 lab abnormalities included increases in INR (2 patients), AST (1), total bilirubin (8, all received ATV/r), and lipase (7, all transient without pancreatitis).

SVR12, % (n/N)	Naive 12 wk	Exp'd 12 wk	Naive 8 wk
All patients	97 (98/101)	98 (51/52)	76 (38/50)
95% CI	89.8, 99.2	88.0, 99.9	59.7, 87.6
GT 1	**96 (80/83)**[a]	98 (43/44)	76 (31/41)
GT 1a	96 (68/71)	97 (32/33)	80 (28/35)
GT 1b	100 (12/12)	100 (11/11)	50 (3/6)
GT 2	100 (11/11)	100 (2/2)	83 (5/6)
GT 3	100 (6/6)	100 (4/4)	67 (2/3)
GT 4	100 (1/1)	100 (2/2)	-
No cirrhosis	98 (88/90)	100 (34/34)	77 (34/44)
Cirrhosis	89 (8/9)	93 (14/15)	60 (3/5)
White race	96 (63/66)	100 (31/31)	71 (20/28)
Black race	100 (30/30)	95 (19/20)	79 (15/19)

[a]Primary endpoint.

Conclusions: DCV+SOF once daily for 12 weeks achieved SVR12 in 97% of patients coinfected with HIV and HCV GT1, 2, 3, or 4, and was safe and well-tolerated.

152LB Ledipasvir/Sofosbuvir for 12 Weeks in Patients Coinfected With HCV and HIV-1

Susanna Naggie[1]; Curtis Cooper[2]; Michael S. Saag[3]; Jenny C. Yang[4]; Luisa M. Stamm[4]; Phillip S. Pang[4]; John McHutchison[4]; Douglas Dieterich[5]; Mark Sulkowski[6]
On behalf of the ION-4 Study Team

[1]Duke Clinical Research Institute, Durham, NC, US; [2]University of Ottawa, Ottawa, Canada; [3]University of Alabama at Birmingham, Birmingham, AL, US; [4]Gilead Sciences, Inc, Foster City, CA, US; [5]Mount Sinai Health System, New York, NY, US; [6]Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: Historically HIV co-infection was considered a negative predictor of HCV response to treatment with interferon/ribavirin (IFN/RBV). For sofosbuvir-based regimens, HIV/HCV patients have achieved similar sustained virologic response (SVR) rates as HCV monoinfected patients. We evaluated the safety and efficacy of the IFN-free, RBV-free, single tablet regimen of ledipasvir/sofosbuvir (LDV/SOF) in HCV genotype 1 or 4 patients co-infected with HIV-1 in the Phase 3 ION-4 study.

Methods: HCV treatment naïve and experienced HIV co-infected patients on stable, approved antiretroviral (ARV) regimens were enrolled and received LDV/SOF (90mg/400mg) once daily for 12 weeks. Patients with compensated cirrhosis were eligible. Permitted concomitant ARVs included tenofovir and emtricitabine (TDF+FTC) with raltegravir (RAL), efavirenz (EFV) or rilpivirine (RPV). Safety evaluations included adverse event (AE) and standard laboratory parameter monitoring in addition to enhanced renal toxicity monitoring, CD4 count and HIV-1 RNA levels. The primary efficacy endpoint was SVR12.

Results: 335 patients with GT1a (75%), GT1b (23%) and GT4 (2%) were enrolled; 82% were male, 61% were white, mean age was 52 (range 26-72), mean baseline HCV RNA was 6.7 $\log_{10}$ IU/mL (range 4.1-7.8), median baseline CD4 count was 662 cells/uL (Q1, Q3=469, 823), 20% had cirrhosis, 24% were *IL28B* CC genotype and 55% had not responded to prior HCV treatment. Patients were taking EFV (48%) or RAL (44%) or RPV (9%). The table shows SVR12 by ARV regimen. Overall, the SVR12 rate was 96% (320/335); 2 patients had on-treatment virologic failure likely due to non-compliance and 10 had virologic relapse after discontinuing treatment. SVR12 was similar among non-cirrhotic (96%) and cirrhotic (94%) patients and also among treatment naïve (94%) and treatment experienced (97%) patients. No patient had confirmed HIV virologic rebound (HIV-1 RNA≥400 copies/mL). No patients discontinued study drug due to an AE. AEs occurring in ≥10% of patients were headache (25%), fatigue (21%) and diarrhea (11%). No significant lab abnormalities were observed.

Virologic Response	TDF+FTC+EFV (N=160)	TDF+FTC+RAL (N=146)	TDF+FTC+RPV (N=29)	Overall (N=335)
SVR12, n (%)	151 (94)	141 (97)	28 (97)	320 (96)
On-Treatment Failure, n (%)	1 (<1)	0	1 (3)	2 (<1)
Relapse, n (%)	8 (5)	2 (1)	0	10 (3)
Other, n (%)	0	3 (2)	0	3 (<1)

SVR12 by HIV ARV regimen and Overall

Conclusions: The IFN-free, RBV-free, single tablet regimen of LDV/SOF administered once daily for 12 weeks is highly effective and well tolerated in treatment-naïve and experienced, genotype 1 or 4 HCV-infected patients with HIV-1 co-infection, including those with cirrhosis.

Session O-13 Oral Abstracts — Room 6D

10:00 am – 12:15 pm

Reaching Populations: Demonstrating Impact

153 Population Viral Load in Three High HIV Prevalence Settings in Sub-Saharan Africa

David Maman[1]; Helena Huerga[1]; Gilles Van Cutsem[2]; Irene Mukui[3]; Benson Chilima[4]; Beatrice Kirubi[5]; Ruggero G. Giuliani[2]; Elisabeth Szumilin[6]; Charles Masiku[7]; Jean-François Etard[1]

[1]Epicentre/Médecins Sans Frontières, Paris, France; [2]Médecins Sans Frontières, Cape Town, South Africa; [3]National AIDS and STDs Control Program, Nairobi, Kenya; [4]Ministry of Health, Lilongwe, Malawi; [5]Médecins Sans Frontières, Nairobi, Kenya; [6]Médecins Sans Frontières, Paris, France; [7]Médecins Sans Frontières, Lilongwe, Malawi

Background: Viral load (VL) is one of the key factors for HIV transmission. However, at population level, little is known about viral load distribution, especially among those undiagnosed or diagnosed but not on treatment. Critical data to better identify those most at risk of transmitting HIV are needed, particularly in sub-Saharan Africa where most of the transmission occurs.

Methods: Three population-based surveys of persons age 15 to 59 were conducted in Ndhiwa (Nyanza, Kenya), Chiradzulu (Malawi) and Eshowe (Kwazulu-Natal, South Africa) between September 2012 and November 2013 to assess HIV incidence and cascade of care. Each individual who agreed to participate was interviewed and tested for HIV at home. All HIV-positive were tested for VL and CD4, regardless of their ART status. T-test was used to compare means VL (in log10 copies/ml). Multivariate linear regression models were fitted to evaluate factors associated with VL among individuals not on ART.

Results: In total 9,802 houses were visited and among 21,782 individuals eligible, 19,006 (87.5%) were included and tested for HIV. Of the 4,117 individuals who tested positive, 3,938 (95.7%) had their viral load assessed. Population viral suppression (VL<1,000copies/ml) was higher in Malawi (61.9%, 95%CI 58.9-64.5) and South Africa (57.1%, 95%CI 54.5-59.6) than in Kenya (40.0%, 95%CI 37.5-42.6).

Of individuals not receiving ART, overall mean VL was higher among men compare to women (4.61 vs 4.17log cp/mLvs, p<0.01) and among those with CD4 between 500 and 749 cells/μL compared to CD4>750cells/μL (4.23 vs 3.72log cp/mL, p<0.01) but was similar across age groups (4.27, 4.37 and 4.22 log cp/mL for age 15-29, 30-44 and 45-59, respectively, p=0.18). Using the multivariate model, men had a VL higher than women (+0.33 log10 cp/mL, 95%CI 0.22-0.43, p<0.01). VL increased with decreasing CD4. CD4 between 500 and 750 CD4 cells/μL was associated with higher VL compared to CD4>750cells/μL (+0.47 log10 cp/mL, 95%CI 0.33-0.61, p<0.01).

Table: Association between risk factors and mean viral load among participants not receiving ART, multivariate linear regression model (n=1,836)

Factors		Number of patients newly diagnosed n=1,836	Adjusted difference in mean viral load in log cp/mL (95% CI)	*p-value*
Gender				
	Women	1,261	Reference	
	Men	575	0.33 (0.23 – 0.43)	<0.01
CD4 (cells/μL)				
	≥750	292	Reference	
	500-749	499	0.47 (0.33 – 0.61)	<0.01
	350-499	445	0.71 (0.57 – 0.86)	<0.01
	50-349	566	1.11 (0.97-1.25)	<0.01
	<49	34	1.03 (0.69-1.38)	<0.01
HIV Status Awareness				
	Not aware	1,101	Reference	
	Aware	735	-0.01 (-0.10 – 0.07)	0.75

* Also adjusted for age, education and marital status

Conclusions: Among individuals not receiving ART, those with CD4 500-750 cells/μL and men had higher viral load and could be at higher risk of transmitting HIV compared to those with CD4>750 cells/μL and women. Targeting men for HIV testing and treatment and ART initiation at higher CD4 thresholds (750 cells/μL) could contribute to decrease HIV transmission.

154 Disparities in Engagement Within HIV Care in South Africa

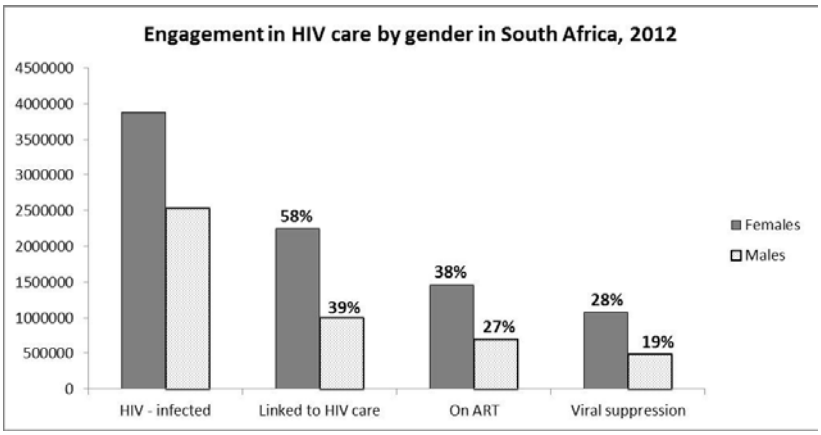
Simbarashe Takuva[1]; Alison Brown[2]; William Macleod[3]; Yogan Pillay[4]; Valerie Delpech[2]; Adrian J. Puren[1]

[1]National Institute for Communicable Diseases, NHLS, Johannesburg, South Africa; [2]Centre for Infectious Diseases Surveillance, Public Health England, London, United Kingdom; [3]Boston University, Boston, MA, US; [4]National Department of Health, Pretoria, South Africa

Background: South Africa (SA) has the largest population of persons living with HIV/AIDS (PLHIVA) in the world. While antiretroviral therapy (ART) provision has rapidly expanded with >2,000,000 people on ART by end of 2012, there were an estimated 400,000 number of new HIV infections in 2012. We characterise engagement within HIV care in 2012 to monitor the effectiveness of the HIV programme and identify areas for improvement.

Methods: National Health Laboratory Service electronic data, a repository for all public sector laboratory measurements in SA were used. Over 3,900,000 CD4 count and viral load measurements conducted in 2012 were extracted, matched then de-duplicated using probabilistic record linkage. The number of PLHIVA was estimated using HIV prevalence estimates from the national household survey. We calculated number and proportion of persons in HIV care, on ART and with viral suppression (viral load<400 copies/ml). We further stratified analysis by gender and age-group. Multivariate regression models were to examine viral suppression rates among those on ART.

Results: Among 6,422,000 PLHIVA in SA in 2012, an estimated 3,300,000 persons (51.4%) accessed care and 34% were on ART. While viral suppression rate was 73.5% among the treated population, the overall percentage of persons with viral suppression among the HIV-infected population was 25.0%, corresponding to potentially 4,500,000 infectious persons. Engagement in care among males was poorer across all stages with only 18.8% with viral suppression (see figure). In the 0-14 age-group, majority in care were on ART (167,000/171,000). Notably, among the sexually active 15-49 year age-group, 47.8% were linked to care, 31.7% were on ART and only 21.5% had viral suppression. Among individuals on ART, males (aPR=0.93, 95%CI 0.93-0.93) and younger persons (aPR=0.94, 95%CI 0.94-0.94; aPR=0.76, 95%CI 0.76-0.76 and aPR=0.77, 95%CI 0.76-0.77 for age-groups 25-49, 15-24 and 0-14 years vs. age 50+ years respectively) were less likely to achieve viral suppression.



Conclusions: Although the number receiving ART has massively increased in SA, an estimated three-quarters of PLWHA have not achieved viral suppression. Expanding HIV testing, strengthening and maintaining prompt linkage to care is crucial. Males and the sexually active 15-49 year age-group have poorer engagement in all stages of care. These groups should be the main focus of prevention efforts as they are potentially driving transmission of new HIV infections in the general population.

155 Decentralizing Access to Antiretroviral Therapy Services for Adults in Swaziland

Andrew F. Auld[1]; Harrison Kamiru[2]; Charles Azih[3]; Andrew L. Baughman[1]; Harriet Nuwagaba-Biribonwoha[2]; Peter Ehrenkranz[1]; Simon Agolory[1]; Tedd V. Ellerbrock[1]; Velephi Okello[3]; George Bicego[1]

[1]US Centers for Disease Control and Prevention, Atlanta, GA, US; [2]ICAP, Columbia University, New York, NY, US; [3]Ministry of Health, Mbabane, Swaziland

Background: In 2007, Swaziland initiated a hub-and-spoke model for decentralizing antiretroviral therapy (ART) access. Decentralization was facilitated through: (1) down-referral of stable ART patients from overburdened central facilities (hubs) to primary healthcare clinics (spokes), and (2) ART initiation at spokes (spoke-initiation). To inform decentralization efforts, a nationally representative retrospective cohort study among adults (≥15 years old) starting ART during 2004–2010, was implemented to assess the effects of down-referral and spoke-initiation on rates of loss to follow-up (LTFU), death, and attrition (death or LTFU).

Methods: Sixteen of 31 ART hubs were randomly selected using probability-proportional-to-size sampling. Seven selected facilities had initiated the hub-and-spoke model by study start. At these facilities, 1,149 of 24,782 hub-initiated and maintained, and 878 of 7,722 down-referred or spoke-initiated patient records were randomly selected. At the nine hub-only facilities, 483 of 6,638 records were randomly selected. Characteristics at ART initiation were compared between hub-only (n=483), hub-initiated and maintained (n=1,149), hub-initiated but down-referred (n=367), and spoke-initiated (n=511) adults. Multivariable proportional hazards regression was used to assess effect of down-referral (a time-varying covariate) and spoke-initiation on outcomes.

Results: At ART initiation, median age was 35, 65% were female, and median CD4 count was 147 cells/μL, with no significant differences in these variables between groups. However, down-referred or spoke-initiated patients tended to have higher median weight, higher functional status, and lower prevalence of tuberculosis treatment at ART start. For down-referred patients, 77% were down-referred after 6 months of ART. Over 5,198 person-years of ART, 107 adults died and 605 were LTFU. Attrition was 20% by 12 months; 3% had died and 16% were LTFU. Controlling for known confounders, down-referral was strongly protective against LTFU [adjusted hazard ratio (AHR) 0.38; 95% CI, 0.29–0.50] and attrition (AHR 0.50; 95% CI, 0.34–0.76) but not mortality. Compared with hub-initiated and maintained patients, spoke-initiated patients had lower LTFU (AHR 0.59; 95% CI, 0.45–0.77) and attrition rates (AHR 0.60; 95% CI, 0.47–0.77), but not mortality.

Conclusions: Down-referral and spoke-initiation within a hub-and-spoke ART decentralization model were protective against LTFU and overall attrition and could facilitate future ART program expansion.

156 Who Are the 10-Year AIDS Survivors on Antiretroviral Therapy in Haiti?

Samuel Pierre[1]; Ashita Batavia[2]; Patrice Severe[1]; Vanessa Rouzier[1]; Benedict Charles[1]; Jean Pape[1]; Warren Johnson[2]; Daniel Fitzgerald[2]; Margaret L. McNairy[2]
On behalf of Les Centres GHESKIO CTU

[1]Les Centres GHESKIO, Port-au-Prince, Haiti; [2]Weill Cornell Medical College, New York, NY, US

Background: Access to antiretroviral therapy (ART) has rapidly expanded over the past decade in resource-limited settings but long-term clinical outcomes of patients, including characteristics of those who have survived for the last decade, have not been reported. We describe the 10-year outcomes and characteristics of the first cohort of patients receiving ART in Haiti.

Methods: Data from 910 ART-naïve patients, age > 13 years, who initiated ART from 2003-4 at GHESKIO were included. Retention was defined as the proportion of patients known to be alive and attending care; lost to follow-up (LTF) was defined as no clinic or pharmacy visit for > 6 months. Cumulative incidence of survival after ART initiation was estimated using Kaplan-Meier methods. Factors associated with LTF and death were assessed using Cox proportional hazard modeling.

Results: Among 910 adults who initiated ART, 55% were female, median age was 38 years (IQR 33-45), and median CD4 was 131 cells/uL (IQR 55-211). Ten years after ART initiation, 477 (52%) patients were retained, 246 (27%) dead, 116 (13%) LTF, and 71 (8%) transferred, with 151 cases of incident TB. The rate of death decreased over time from 25 deaths/100 PY in the first 6 months to 3.60/100 PY (6 months to 5 years) and 1.32/100PY (5 to 10 years). Predictors of death in the first 6 months were age > 50, lowest quartile weight, CD4 < 50 cells/uL, WHO stage III/VI and baseline TB. Death after 6 months was associated with age, both 13-24 and > 50 age groups, and lowest quartile weight. The rate of LTF decreased from 3.91/100 PY in the first 6 months to 1.36/100 PY (6 months to 5 years) and 1.82/100PY (5 to 10 years). Lowest quartile weight was associated with LTF across the 10 years. Among the 473 persons alive and in care at 10 years, median age was 49 (IQR 43-55), 57% were female, median CD4 was 541 cells/uL, and 74% were on first-line therapy. 177 survivors (25%) had documentation of a non-communicable disease (195 cases: 58% hypertension, 3% diabetes, and 39% chronic lung disease).

Conclusions: This analysis documents the long-term effectiveness of an ART program among the first cohort of patients to receive ART in the Caribbean and Latin American Region. Excellent retention and a lower death rate were observed during the 5 to10 year follow-up period as compared to the first 5 years. High prevalence of non-communicable diseases among this population points to the changing needs of aging populations on ART.

157 Nationwide Evaluation of Antiretroviral Therapy Coverage on Prevention in Rwanda: A Multisectional Time-Trend Analysis

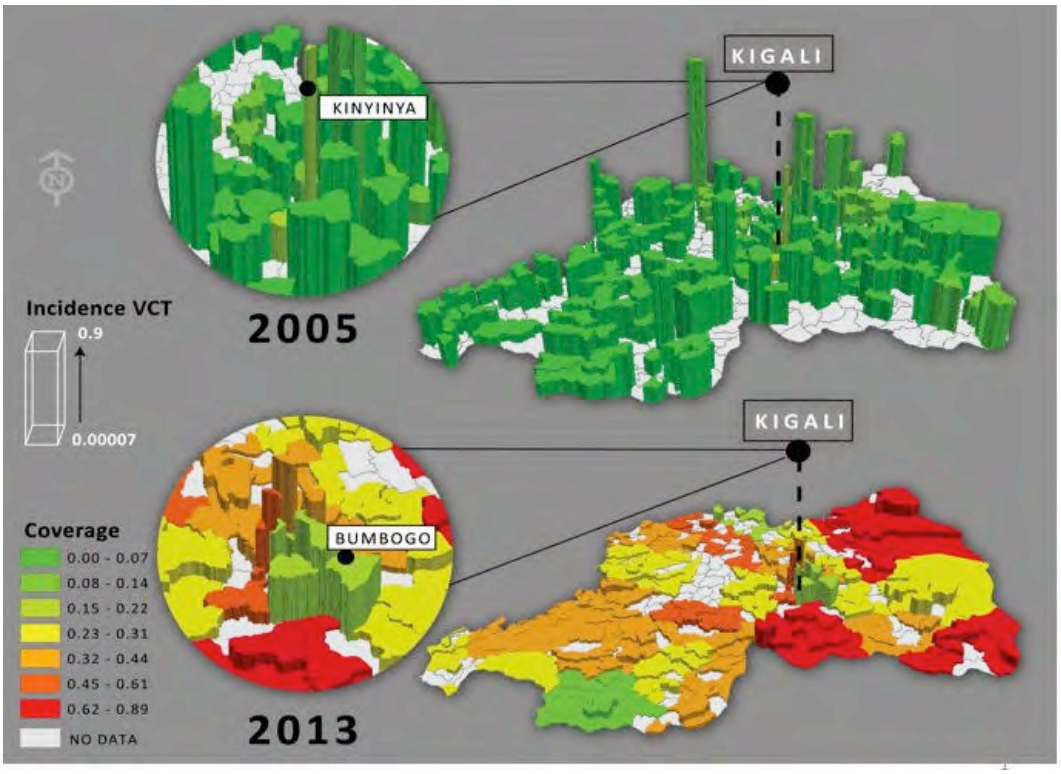
Sabin Nsanzimana[2]; Eric Remera[2]; Steve Kanters[1]; Eric Dusabe[2]; Adeline Dukuze[2]; Till Barnighausen[3]; Eran Bendavid[1]; Julio Montaner[4]; **Edward Mills**[1]
On behalf of the Rwanda Treatment as Prevention Working Group

[1]Stanford University, Vancouver, Canada; [2]Rwanda Biomedical Centre, Kigali, Rwanda; [3]Harvard School of Public Health, Boston, MA, US; [4]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada

Background: Rwanda is one of the most successful countries in terms of antiretroviral therapy (ART) coverage and recently changed guidelines to immediately initiate ART for key groups and at CD4 status of 500 cells/mm^3 among the general population. We aimed to examine the effect of treatment scale-up on the incidence of new infections using a time-staggered causal design.

Methods: We applied a Bayesian hierarchical design that assessed the scale-up of ART across 416 health sectors among 30 districts in Rwanda. We assess the number of infections detected within these health sectors in three-month periods over ten years (2004-2014). We assessed the projected number of new infections per health sector and modeled the change in slope between cases detected and projected cases. We used three different methods to evaluate incidence within each health sector.

Results: In our study period, 123,317 patients initiated ART across Rwanda. Figure 1 displays the reduction in VCT detection and increase in coverage between 2005 and 2013. New cases detected peaked in 2007 and reduced to 12,993 in 2013. We found that for every 10% increase in coverage per health sector, a 6.07 percent reduction in incidence occurred. At the current coverage of 50% of all eligible patients in Rwanda, the effect of ART has contributed a reduction of 26.9% (95% Confidence Intervals [CI] 21.9-31.9%) year by year in a multiplicative way – increasing to 71% by four years. The new target goal of providing ART at 500 cells/mm^3 is estimated to reduce incidence by 36% per year (83% in four years).



Change in positive HIV test detection and ART coverage between 2005 and 2013.

Conclusions: This is, to our knowledge, the first nation-wide evaluation examining the effect of ART on incidence. Our findings demonstrate a large preventive effect associated with ART coverage. As scale-up to new guidelines and targeted populations increase, the preventive effects of ART coverage will likely contribute to greater declines in population incidence.

158 Impact of Male Circumcision Scale-Up on Community-Level HIV Incidence in Rakai, Uganda

Xiangrong Kong[1]; Godfrey Kigozi[2]; Fred Nalugoda[2]; David Serwadda[3]; Maria J. Wawer[1]; Ronald H. Gray[1]
On behalf of the Rakai Health Sciences Program

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]Rakai Health Sciences Program, Entebbe, Uganda; [3]Makerere University College of Health Sciences, Kampala, Uganda

Background: Randomized trials show male circumcision (MC) reduces individual level risk of HIV acquisition by 50-60% in men, and MC has been scaled up in sub-Saharan Africa. We assessed the impact of MC coverage on community level HIV incidence among non-Muslim men in Rakai, Uganda.

Methods: The Rakai Community Cohort Study (RCCS) conducts ~ annual surveillance of consenting residents aged 15-49 in 43 rural communities consistently since 1999. Before 2003, MC was largely confined to Muslim men. MC services to non-Muslims were provided through randomized trials during 2004-07 and were scaled up via a PEPFAR program since 2008. For each community, the non-Muslim male population prevalence of MC and HIV incidence per 100 person years (py) was estimated before the MC trials (period 1: 1999 -2003), during the trials (period 2: 2004-07), and since the MC scale up (period 3: 2008-11). Incidence rate ratio (IRR) of community level (CL) HIV incidence associated with CL MC prevalence was estimated by Poisson log-linear regression. Adjusted IRR was also estimated adjusting for potential confounding due to potential population composition change over time (measured by the surrogate of time periods) and CL ART coverage among HIV+s.

Results: In period 1, the mean CL HIV incidence among non-Muslim men was 1.4/100pys (range 0-4.1/100pys); and mean CL MC prevalence was 4.1% (range 1-8%). ART was not available during this period. In period 2, the mean CL HIV incidence was 0.9/100pys (range 0-3.7/100pys), mean CL MC prevalence was 10.0% (range 0-30%), and the mean CL ART prevalence was 5.2% (range 0-13%). In period 3, the mean CL HIV incidence was 1.1/100pys (range 0-3.6/100pys), mean CL MC prevalence was 23.5% (range 0-45%), and mean ART prevalence was 17.9% (range 3-42%). For every 10% increase in CL MC prevalence among non-Muslims, the associated IRR of CL HIV incidence was 0.85 (p=0.006, 95% Confidence Interval [CI] 0.75-0.95). After adjusting for time period and CL ART prevalence, CL MC prevalence had an adjusted IRR of 0.81 (p =0.076, 95% CI 0.65-1.02).

Conclusions: The MC program reached 23.5% coverage among non-Muslim men in Rakai by 2011, with large variations across communities. A 10% increase in community level MC coverage was associated with a 15% (95%CI 5-25%) reduction in CL HIV incidence among non-Muslim men, and this reduction of CL HIV risk was robust after adjusting for potential confounding due to time period and CL ART coverage.

159 Effects of Antiretroviral Treatment on Health Care Utilization in Rural South Africa

Jan A. Hontelez[1]; Frank Tanser[2]; Sake J. de Vlas[1]; Kevindra K. Naidu[2]; Rob Baltussen[3]; Deenan Pillay[2]; Till Barnighausen[2]

[1]Erasmus University Medical Center, Nijmegen, Netherlands; [2]Africa Centre for Health and Population Studies, Somkhele, South Africa; [3]Radboud University Medical Centre, Nijmegen, Netherlands

Background: The impact of the rapid scale-up of vertical antiretroviral treatment (ART) programs for HIV in sub-Saharan Africa on the overall health system is under intense debate. Some argue that HIV treatment programs are draining resources for the treatment of other diseases, while others have claimed that the investments through ART programs benefitted the health system. To establish the population-level impact of ART programs on health care utilization in the public-sector health system, we compare trends in health care utilization among HIV-infected people receiving and not receiving ART with HIV-uninfected people during a period of rapid ART scale-up.

Methods: We used data from one of Africa's largest population-based cohorts, the longitudinal surveillance conducted by the Wellcome Trust Africa Centre for Health and Population Studies, which annually elicits information on health care utilization from all surveillance participants over the period 2009-2012 (N=44,461). We determined trends in hospitalization, and public and private primary health care (PHC) clinic visits for HIV-infected and -uninfected people over the period 2009-2012, and regressed utilization rates by HIV and ART status over time, controlling for sex, age, time on ART, and area of living.

Results: The proportion of people who reported to have visited a PHC clinic in the last 6 months increased significantly over the period 2009-2012, for both HIV-infected people not on ART (from 53% to 60%; p<0.001), and HIV-uninfected people (from 41% to 47%; p<0.001) (figure 1A). In contrast, the proportion of HIV-infected people not on ART visiting a private physician declined from 21% to 13% (p<0.001) (figure 1B) and hospitalization rates declined from 100 to 71 per 1000 PY (p<0.001) (Figure 1C). For HIV-uninfected people, the proportion visiting a private physician declined from 15% to 9%, and hospitalization rates declined from 78 to 44 per 1000 PY (p<0.001). All trends were sustained when controlling for potential confounders.

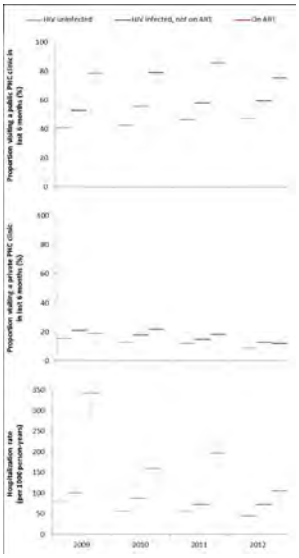


Figure 1. Trend in age-standardized self-reported health care utilization by HIV and ART status over the years 2009 to 2012 in rural KwaZulu-Natal, South Africa. A. Proportion of people reporting to have visited a public PHC clinic in the last 6 months. **B.** Proportion of people reporting to have visited a private PHC clinic in the last 6 months. **C.** Self-reported hospitalization rates over the last 12 months

Conclusions: Our results do not support the claim that ART program scale-up lead to reduced access to care for other diseases. In contrast, the ART program has freed up secondary care capacity and has likely improved both the effectiveness and efficiency of the public-sector health system by channelling utilization from secondary to primary care in this setting. Future health systems interventions should build on these trends to improve the performance of chronic disease management in public-sector primary care.

160 The Impact of PEPFAR Abstinence and Faithfulness Funding Upon HIV Risk Behaviors in Sub-Saharan Africa

Nathan C. Lo; Anita Lowe; Eran Bendavid

Stanford University School of Medicine, Stanford, CA, US

Background: The United States President's Emergency Plan for AIDS Relief (PEPFAR) supports more abstinence and faithfulness programs in sub-Saharan Africa than any other funder. We assess the relationship between PEPFAR's support for these programs and changes in high-risk sexual behavior. Evaluating the outcomes of foreign aid for HIV is important for optimizing HIV treatment and prevention portfolios.

Methods: Using individual-level nationally-representative survey data from the Demographic and Health Surveys for 22 sub-Saharan African countries, we employed a difference-in-differences analysis to assess the relationship of PEPFAR abstinence and faithfulness funding to changes in three outcomes indicative of high-risk sexual behaviors: the number of sexual partners, age of first sexual intercourse, and teenage pregnancies. We compare trends in these outcomes among persons living in PEPFAR funded and non-PEPFAR countries from 1998 to 2013.

Results: We analyzed 252,251 men and 591,714 women using 54 surveys in 14 PEPFAR funded and 8 non-PEPFAR funded countries. In comparison with non-PEPFAR countries, survey respondents living in PEPFAR countries exhibited no relative change in the number of sexual partners among men (0.02 more partners; 95% CI (-0.04, 0.08); p=0.48), number of sexual partners among women (0.02 fewer partners; 95% CI (-0.05, 0.01); p=0.15), age of first sex among men (0.10 years earlier; 95% CI (-0.91, 0.70); p=0.79), age of first sex among women (0.19 years earlier; 95% CI (-0.76, 0.37); p=0.49), or in rates of teenage pregnancy (2% relative decline in prevalence; 95% CI (-7, 2%); p=0.34).

Table: Regression model estimating the changes in high-risk sexual behavior in PEPFAR versus non-PEPFAR countries

	Number of sexual partners, male			
N=251,251	Unadjusted coeff (95% CI)	P-value	Adjusted coeff (95% CI)	P-value
PEPFAR funding	0.10 (-0.07, 0.26)	0.23	0.02 (-0.04, 0.08)	0.48
Education				
Primary education			0.04 (-0.02, 0.10)	0.15
Beyond primary education			0.08 (-0.02,0.18)	0.12
Residence in rural area			0.00 (-0.03, 0.03)	0.93
	Number of sexual partners, female			
N=591,714	Unadjusted coeff (95% CI)	P-value	Adjusted coeff (95% CI)	P-value
PEPFAR funding	-0.04 (-0.08,0.01)	0.11	-0.02 (-0.05, 0.01)	0.15
Education				
Primary education			-0.03 (-0.06, 0.01)	0.13
Beyond primary education			-0.09 (-0.14, -0.04)	<0.01
Residence in rural area			0.01 (-0.01, 0.03)	0.31
Wealth (ownership of car)			-0.03 (-0.04, -0.01)	<0.001
	Age at first sex, male			
N=73,501	Unadjusted coeff (95% CI)	P-value	Adjusted coeff (95% CI)	P-value
PEPFAR funding	0.41 (0.06, 0.76)	0.02	-0.10 (-0.91, 0.70)	0.79
Education				
Primary education			-0.41 (-0.63, -0.19)	<0.01
Beyond primary education			-0.36 (-0.55, -0.18)	<0.01
Residence in rural area			-0.23 (-0.35, -0.11)	<0.01
	Age at first sex, female			
N=179,366	Unadjusted coeff (95% CI)	P-value	Adjusted coeff (95% CI)	P-value
PEPFAR funding	0.23 (-0.05, 0.51)	0.10	-0.19 (-0.76, 0.37)	0.49
Education				
Primary education			0.19 (-0.07, 0.44)	0.14
Beyond primary education			0.90 (0.67, 1.13)	<0.001
Residence in rural area			-0.36 (-0.46, -0.26)	<0.001
Wealth (ownership of car)			0.31 (0.25, 0.37)	<0.001
	Teenage pregnancy			
N=170,399	Marginal effects (95% CI)	P-value	Adjusted marginal effects (95% CI)	P-value
PEPFAR funding	-0.03 (-0.06, 0.01)	0.16	-0.02 (-0.07, 0.02)	0.34
Education				
Primary education			-0.01 (-0.07, 0.06)	0.80
Beyond primary education			-0.21 (-0.28, -0.15)	<0.001
Residence in rural area			0.07 (0.05, 0.09)	<0.001
Wealth (ownership of car)			-0.11 (-0.13, -0.09)	<0.001

Note: Country-level covariates of GDP per capita (USD), population (millions), and contraception prevalence were included in analysis, but not shown in table due to near-zero coefficients and statistical insignificance.

Conclusions: We find no evidence to suggest that PEPFAR funding of abstinence and faithfulness programs results in reduced high-risk sexual behavior. These results suggest the importance of examining alternative funding priorities for PEPFAR to improve HIV prevention in sub-Saharan Africa.

161 The Impact of Antiretroviral Therapy on Adult Life Expectancy in Sub-Saharan Africa

Georges Reniers[8]; Jeffrey Eaton[1]; Jessica Nakiyingi-Miiro[2]; Amelia C. Crampin[4]; Chodziwadziwa Kabudula[5]; Kobus Herbst[3]; Mark Urassa[6]; Amek Nyaguara[7]; Emma Slaymaker[8]
ALPHA Network

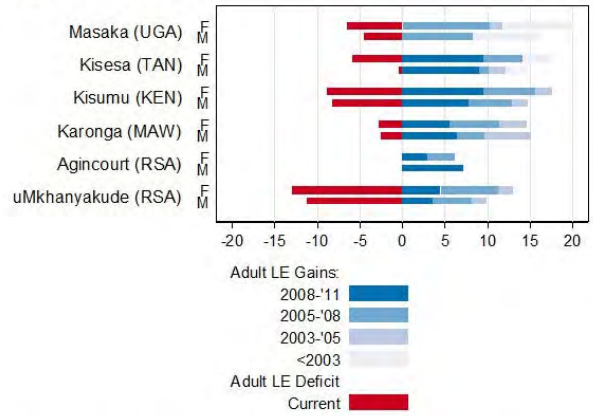
[1]Imperial College London, London, United Kingdom; [2]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda; [3]Africa Centre for Health and Population Studies, Mtubatuba, South Africa; [4]Karonga Prevention Study, Chilumba, Malawi; [5]University of the Witwatersrand, Johannesburg, South Africa; [6]National Institute for Medical Research, Mwanza, United Republic of Tanzania; [7]Kenya Medical Research Institute-Centers for Disease Control, Kisumu, Kenya; [8]London School of Hygiene and Tropical Medicine, London, United Kingdom

Background: Few studies directly measure the population-wide impact of antiretroviral therapy (ART) on adult mortality, with most existing estimates relying on extrapolations from ART coverage. We use demographic surveillance data from seven study sites in six eastern and southern African countries to estimate (i) gross adult life expectancy (LE) gains since the introduction of ART, (ii) net LE gains attributable to ART, and (iii) the remaining LE deficit due to HIV.

Methods: We use non-parametric survival analysis for estimating the LE of adults aged 15 years and above. The gross LE gain is defined as the difference in the overall LE between two calendar years; the current LE deficit due to HIV is the difference in the LE of HIV negatives and the LE for the population as a whole. Net LE gains attributable to ART are obtained by fitting a model of age-specific HIV incidence and survival to estimate the counterfactual LE in the absence of ART. Estimates are presented for the years 2000 to 2012, and disaggregated by sex and study site.

Results: The pooled dataset contains 655,227 adults, contributing over 3 million person-years of follow up time and 46,898 deaths. Gross adult LE gains range from 8 to 20 years (Figure 1); net LE increases attributable to ART are between 4 and 19 years. Gross LE gains are largest in eastern Africa, where mortality reductions also benefited from historical declines in HIV incidence, but the effect of ART (net LE gains) is largest in South Africa, where LE would have continued to decline without ART. The current LE deficit is around 10 years in sites with the highest HIV prevalence (Kisumu and uMkhanyakude); in other sites the LE deficit is now under 5 years (Figure 1). On average, women have gained 3.4 more adult life-years than men, but their current LE deficit is still between 0.6 and 5.4 years larger.

Figure 1: The gross adult LE gains to date (blue) and the current LE deficits (red), by sex (F/M) in six ALPHA Network study sites



Notes: The LE deficit cannot be computed Agincourt because HIV status information is only available for a small sample. Estimates for Manicaland (ZIM) are in preparation.

Conclusions: Gross adult LE gains between 10 and 15 years are norm and driven by the expansion of treatment, and in the eastern African study sites also by prior declines in HIV incidence. Large LE deficits due to HIV remain, however, and are indicative of the need for enhancing program coverage and impact. Women have generally gained more life-years than men, and that is due to gender differences in the uptake of services and treatment outcomes, women's younger ages at infection, and women's lower background mortality. Despite larger LE gains to date, women still lose more life-years to HIV than men.

Session O-14 Oral Abstracts — Room 613

10:00 am – 12:15 pm

Immune Mechanisms: The Road to Protection

162 Passively Acquired ADCC Activity in HIV-Infected Infants Correlates With Survival

Caitlin Milligan[1]; Barbra A. Richardson[1]; Grace John-Stewart[2]; Ruth W. Nduati[3]; Julie M. Overbaugh[1]

[1]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [2]University of Washington, Seattle, WA, US; [3]University of Nairobi, Nairobi, Kenya

Background: Antibody-dependent cellular cytotoxicity (ADCC) activity has been described as a potential immune correlate of protection from HIV infection in macaques and humans. The role of ADCC activity mediated by passively acquired antibodies (Abs) in HIV-exposed infants is unknown and was examined to determine if pre-existing HIV-specific antibodies provide protection from infection and/or disease progression.

Methods: We evaluated the ADCC activity of passively acquired Abs in the first week of life from infants of HIV-positive mothers. Infants were included based on the following criteria: HIV-RNA negative at birth, breastfed ≥3 months, ≥6 months follow-up of negative infants. Seventy-two infants were included, 21 of who were first detected as HIV positive after birth. Infant plasmas were tested against an infant-derived, subtype A envelope using a rapid fluorometric ADCC assay. HIV-specific IgG1 was measured by binding to gp120 coated target cells and quantified by flow cytometry. IgG3 HIV-specific Ab titers were measured by ELISA. Comparisons of measurements in infected and uninfected infants were made by 2-sided Welch's t-test. Survival analyses were conducted using Cox-proportional hazards models. Spearman's rank correlation was used for correlation analyses.

Results: Passively acquired ADCC activity was higher in uninfected infants than infected infants, but was not statistically significant (p=0.12). In infected infants, pre-existing ADCC activity was associated with increased survival: each 10% increase in ADCC activity was associated with a 49.1% reduction in the risk of mortality (p=0.03). ADCC activity positively correlated with the magnitude of HIV-specific IgG1 surface binding, measured as $\log_2$MFI(r=0.92, p<0.0001). The magnitude of surface IgG1 binding was also associated with survival in infected infants (HR:0.24, p=0.005). IgG3 binding Ab end point titers were not associated with infant infection (p=0.25) or survival (p=0.63). In measurements of longitudinal ADCC activity from 6 infected infants, passively acquired ADCC activity declined to undetectable levels prior to an increase in *de novo* responses. *De novo* ADCC responses did not correlate with passively acquired responses (r=-0.14, p=0.79).

Conclusions: These data suggest that HIV-specific, ADCC-mediating passively acquired Abs may impact disease progression and survival among infected infants. In particular, IgG1 and not IgG3 Abs appear to be responsible for the effect and *de novo* responses do not explain the survival benefit.

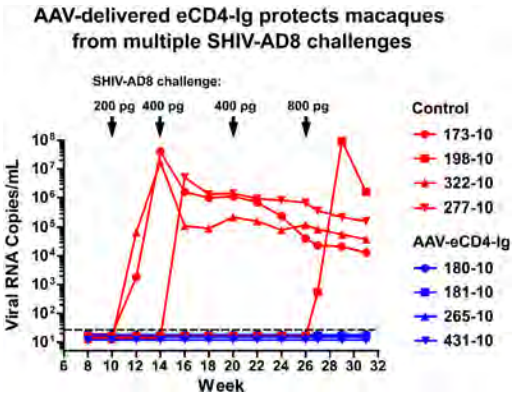
163 AAV-Expressed eCD4-Ig Protects Rhesus Macaques From Multiple SHIV-AD8 Challenges

Michael Farzan
The Scripps Research Institute, Jupiter, FL, US

Background: Long-term *in vivo* expression of a broad and potent entry inhibitor could circumvent the need for a conventional HIV-1 vaccine. Adeno-associated virus (AAV) vectors can stably express broadly neutralizing HIV-1 antibodies (bNAbs). However, more than a quarter of HIV-1 isolates are at least partially resistant ($IC_{80} > 5$ μg/ml) to even the best bNAbs, suggesting that very high concentrations of these antibodies would be necessary to achieve general protection.

Methods: Here we characterize eCD4-Ig, a fusion of CD4-Ig with a small CCR5-mimetic sulfopeptide, and assess AAV-delivery of eCD4-Ig as a means of stably protecting individuals from a new HIV-1 infection.

Results: We show that eCD4-Ig binds avidly and cooperatively to the HIV-1 envelope glycoprotein (Env) and is more potent than the best bNAbs (geometric mean $IC_{50} < 0.05$ μg/ml). Because eCD4-Ig only binds conserved regions of the Env, it is also much broader than any bNAb. For example, eCD4-Ig neutralized 100% of a diverse panel of neutralization-resistant HIV-1, HIV-2, and SIV isolates with IC_{80}s less than 5 μg/ml, including a comprehensive set of isolates resistant to the CD4-binding site bNAbs VRC01, NIH45-46, and 3BNC117. Rhesus macaques inoculated with an AAV vector expressed 16-84 μg/ml of fully functional rhesus eCD4-Ig over 32 weeks, and these macaques were protected from multiple challenges with SHIV-AD8 that efficiently infected control macaques. Moreover, eCD4-Ig was markedly less immunogenic than any of four well characterized bNAbs.



Conclusions: AAV-expressed eCD4-Ig can function as an effective HIV-1 vaccine alternative.

164LB HIV Neutralizing Antibodies Induced by Native-Like Envelope Trimers

Rogier Sanders
The WCMC/Scripps/AMC HIVRAD team
Academic Medical Center University of Amsterdam, Amsterdam, Netherlands

Background: Inducing HIV-1 neutralizing antibodies against neutralization-resistant (Tier-2) virus strains has been a challenge.

Methods: Our working hypothesis has been that stable native-like envelope trimers should induce neutralizing antibodies (NAbs).

Results: We show here that such trimers based on the pediatric founder virus BG505 (BG505 SOSIP.664 gp140), consistently induced neutralizing antibodies (NAbs) against the autologous, neutralization-resistant (Tier-2) BG505.T332N virus at high titers in rabbits and macaques. Cross-reactive NAbs against more sensitive (Tier-1) viruses were also induced. The Tier-1 and the autologous Tier-2 NAb responses were uncorrelated, implying that different pathways and B-cell subsets are involved. Tier-1 NAbs were depleted by linear V3 peptides, while Tier-2 NAbs recognized several conformational epitopes that differed between animals, that sometimes involved glycosylation sites and that were similar to some broadly active NAb epitopes. We have designed amino acid substitutions that further stabilize and antigenically improve BG505 SOSIP.664 trimers. The same substitutions also allowed the generation of stable native-like trimers based on virus isolates from clades B and C, including a clade B isolate from an elite neutralizer that developed broad neutralization within 9 months post seroconversion. Finally, we designed a stable native-like trimer that is able to interact with the germline versions of diverse bNAbs.

Conclusions: These rationally designed trimers represent suitable starting points for lineage and/or polyvalent vaccines aimed at inducing NAbs able to counter diverse Tier-2 isolates.

165 Efficacy Loss of BnAbs During HIV-1 Cell-Cell Spread Is Strain- and Epitope-Dependent

Lucia Reh; Carsten Magnus; Merle Schanz; Jacqueline Weber; Therese Uhr; Peter Rusert; Alexandra Trkola
University of Zurich, Zurich, Switzerland

Background: HIV-1 cell-cell transmission promotes high efficacy of infection, which inflicts a dramatic loss in neutralization potency even by broadly neutralizing antibodies (bnAbs) compared to free virus infection. A precise definition of inhibitory potentials during cell-cell transmission is therefore needed to select bnAbs that are capable of suppressing HIV irrespective of the transmission mode, securing in vivo activity and allowing for their use as vaccines and in passive immunization.

Methods: We have compiled assay systems that allow for unambiguous discrimination between free virus and cell-cell transmission. For this, PBMC or CD4+ CCR5+ A3.01 T cells were co-cultured with producer cells (PBMC or 293-T cells), either infected with replication competent virus or transfected with env pseudotyped inGLuc reporter viruses to distinguish cell-cell transmission from fusion events. Inhibitory capacities of the bnAbs (b12, VRC01, NIH45-46, 3BNC117, PGV04, PGTs 121, 125, 128, 135, 145, PG9, PG16, 2G12, 10E8, 2F5, 4E10) during cell-cell transmission of HIV-1 strains from subtypes A, B and C were studied and their potency to block virus transmission pre and post CD4 engagement was assessed.

Results: Across almost all bnAb-virus combinations tested, the potency to inhibit HIV-1 cell-cell transmission was strongly decreased compared to free virus transmission. However, loss of potency varied considerably between virus strains and strikingly, high potency against free virus did not ensure lower loss in activity during cell-cell transmission.

In rare bnAb-virus combinations, inhibition capacities proved comparable for both transmission modes but no bnAb that potently blocked cell-cell transmission over a range of HIV-1 strains could be identified. Likewise, the capacity of bnAbs to block HIV infection post CD4 engagement differed among virus strains and bnAbs tested.

Importantly, mathematical analysis employed to estimate the consequences of the observed activity loss during cell-cell transmission indicated an increased probability of viral resistance mutations to arise in cell-cell rather than free virus spread.

Conclusions: Our data suggest that the efficacy of bnAbs during cell-cell transmission cannot be predicted by their free virus activity and greatly differs in a strain-dependent manner. Potent inhibition of both transmission routes will only be possible through a combination of bnAbs, either by multi-component vaccines or antibody cocktails in passive immunization.

166 Peripheral T Follicular Helper Cells With Universal Helper Activity in HIV Infection

Bruce Schultz; Alexander Oster; Franco Pissani; Jeffrey E. Teigler; Michael A. Eller; Merlin L. Robb; Jerome H. Kim; Nelson L. Michael; Diane Bolton; **Hendrik Streeck**

US Military HIV Research Program, Silver Spring, MD, US

Background: Immunogen design to generate protective neutralizing antibodies is a central effort in HIV vaccine development and critically dependent on T follicular helper (T_{FH}) cells. However, very little is known about the peripheral counterpart of HIV-specific T_{FH} cells and the protein-specific help they might provide.

Methods: Biomark Fluidigm gene expression profiles from HIV-specific IL-21+ and IFNγ+ CD4 T cells were analyzed from chronic, treatment-naïve HIV-infected individuals. Epitope specificity of peripheral T_{FH} cells and Th1 cells was defined by Elispot. HIV-specific T_{FH} cell lines were generated and their functionality and phenotype assessed by flow cytometry. Helper activity of Gag-and Env-specific T_{FH} cells were tested in a CD4-B cell as well as CD4-CD8 T cell co-culture assay. HIV-specific T_{FH} responses from ALVAC/AIDSVAX and DNA/Ad5 vaccine recipients were also compared.

Results: HIV-specific IL21+CD4 T cells showed significantly higher expression of genes associated with T_{FH} cells compared to IFNγ+ or IL21+/IFNγ+ CD4 T cells including BCL6, cMaf and CXCR5. IL21+CD4 T cells most closely resembled T_{FH} cells compared to any other phenotypic description of pT_{FH} cells. Besides CXCR5+, HIV-specific pT_{FH} cells predominantly expressed ICOS and PD1 but were CCR7-. The frequency of HIV-specific pT_{FH} cells was low when compared to HIV-specific IFNγ+CD4 cells ($p<0.0001$). Interestingly, while HIV-specific IFNγ+CD4 T cells dominantly targeted epitopes in Gag, HIV-specific T_{FH} cells equally recognized epitopes within Gag and Env ($p=0.0009$). Gag- and Env-specific T_{FH} cells were able to provide help to HIV-specific CD8 T cells *in vitro*, characterized by Perforin/GrzB induction. In contrast, however, Gag-specific T_{FH} cells preferentially induced maturation and proliferation of B cells, while Env-specific T_{FH} cells predominantly drove Ig class switching. Further analysis revealed that Env-specific T_{FH} cells also displayed features indicative of Th2 cells compared to Gag-specific T_{FH} responses ($p=0.0003$). Lastly, we found that ALVAC/AIDSVAX vaccine recipients had significantly higher levels of HIV-specific pT_{FH} cells but comparable levels of HIV-specific Th1 cells as DNA/Ad5 vaccine recipients.

Conclusions: Given the evidence presented here for the role that IL21+CD4 T cells appear to play in the maturation of vaccine evoked humoral immune responses, these findings have clear implications for HIV vaccine design.

167 Redirected Killing of HIV-Infected T Cells by Germinal Center CD8 T Cells

Constantinos Petrovas[1]; Sara Ferrando-Martinez[1]; Michael Gerner[2]; Amarendra Pegu[1]; Perla Del Río-Estrada[3]; Kristin Boswell[1]; Manuel Leal[4]; Gustavo Reyes-Teran[3]; Ronald Germain[2]; Richard A. Koup[1]

[1]Vaccine Research Center, National Institute of Allergy and Infectious Diseases, Bethesda, MD, US; [2]NIAID-NIH, Bethesda, MD, US; [3]Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico; [4]Instituto de Biomedicina de Sevilla, Sevilla, Spain

Background: Follicular helper CD4 T cells (T_{FH}) are located within the germinal centers (GC) of lymph nodes (LN) and represent a major contributor to the latent reservoir. Bispecific antibodies that target HIV Env and CD3 are being developed to eliminate the latent reservoir by activating HIV from CD4 T cells and inducing killing of those cells by CD8 T cells. We characterized the localization, frequency, and function of CD8 T cells in GCs to determine if they were present and capable of killing HIV-expressing cells in the context of HIV Env/CD3-targeting bispecific antibodies.

Methods: The phenotype, localization and function of CD8 T cells in tonsils and LNs from non-infected and HIV-infected viremic individuals was investigated. Polychromatic flow cytometry was used for phenotypic analysis and confocal imaging for spacial localization. Histo-Cytometry was performed for the quantitative analysis of GC cell populations. Function (IFN, TNF, MIP-1, and Perforin, GzB production) was assessed by intracellular staining after stimulation with anti-CD3. (5 hour). In vitro cytolytic activity of sorted CD8 T cell populations was tested in a killing assay using an anti-HIV Env/anti-CD3 bispecific-antibody. Cytokines and soluble cell death mediators were analyzed by Luminex.

Results: Phenotypic analysis of tonsillar cells revealed a memory population of CD8 T cells expressing a $CCR7^{low}CXCR5^{high}$ profile compatible with follicular localization. Histo-Cytometry analysis confirmed the presence of a small population of CD8 T cells within the GC. These GC CD8 T cells were expanded in HIV-infected LNs compared to non-infected tonsils. Follicular CD8 T cells (defined by CXCR5 expression and loss of CCR7) exerted a superior killing capacity judged by in vitro mobilization of GzB/Perforin. Production of MIP-1 and GzB predominated over IFN and TNF production in GC CD8 T cells. Of all tissue CD8 T cell populations tested, GC localized CD8 T cells had the greatest ability to mediate killing of HIV-infected target cells after cross-linking with an anti-HIV Env/anti-CD3 bispecific antibody.

Conclusions: HIV infection is characterized by accumulation of CD8 T cells within LN follicles. These CD8 T cells are functionally capable of mediating bispecific antibody-mediated killing of HIV-infected CD4 T cells. These data add credence to the use of bispecific antibody therapy to purge the LN reservoir

168 IL-21 Reduces Inflammation and Virus Persistence in ART-Treated SIV-Infected Macaques

Luca Micci[1]; Emily Ryan[1]; Colleen McGary[1]; Sara Paganini[1]; Guido Silvestri[1]; Mike Piatak[2]; Jeffrey Lifson[2]; Francois Villinger[1]; Jason M. Brenchley[3]; Mirko Paiardini[1]

[1]Yerkes National Primate Research Center, Emory University, Atlanta, GA, US; [2]Leidos Biomedical Research, Inc, Frederick, MD, US; [3]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

Background: Residual inflammation persists and critically contributes to non-AIDS-related morbidity/mortality in ART-treated, HIV-infected subjects. Furthermore, inflammation may contribute to HIV persistence during ART. Interleukin (IL)-21 regulates the differentiation and maintenance of IL-17- and IL-22- producing CD4 T cells, which depletion critically contributes to chronic immune activation and disease progression in HIV and SIV infection. In this study, we investigated the effects of Interleukin (IL)-21 administration in chronic, ART-treated SIV-infected rhesus macaques (RMs) on mucosal integrity, residual inflammation, and virus persistence.

Methods: Sixteen RMs were infected with SIV_{mac239} i.v. and, starting at day 60 post-infection, treated for seven months with PMPA, FTC, Raltegravir, Darunavir and Ritonavir. Eight RMs received IL-21-Fc (100 mg/kg, s.c., weekly for six weeks) at the beginning and the end of ART, with the other eight serving as ART- treated controls. Blood, lymph nodes and rectum were longitudinally collected, and the effects of IL-21 on inflammation, T cell subset levels, and viral persistence assessed. The Mann-Whitney test was used for statistical analyses.

Results: ART was very effective, with fully suppressed plasma viremia (<60 SIV-RNA copies/ml) in all RMs. Compared to ART-controls, ART+IL-21 RMs showed improved restoration of intestinal Th17 and Th22 cells ($P<0.01$ for both subsets). Remarkably, IL-21-treated RMs showed a faster and more pronounced reduction in the levels of activated ($HLA\text{-}DR^{+}CD38^{+}$) and proliferating ($Ki\text{-}67^{+}$) T cells in rectum and blood during ART ($P<0.01$), and maintained level of T cell activation significantly lower than controls up to eight months following ART-interruption ($P<0.01$). Between days 75 to 200 on-ART, IL-21-treatment elicited a higher number of RMs with undetectable (<3 copies/mL) SIV-vRNA in

plasma (P<0.03). Furthermore, rectal cell associated SIV-DNA levels were significantly reduced between d75 and d200 on-ART in IL-21-treated RMs (P<0.01) but not in controls. Finally, only IL-21-treated animals maintained plasma viral loads significantly lower than those at pre-ART up to eight months post-ART interruption.

Conclusions: These data provide evidence of a link between mucosal immunity, inflammation, and HIV persistence. Furthermore, they suggest that IL-21 may provide important therapeutic benefits when used as an adjunctive immunomodulatory agent in ART-suppressed HIV-infected individuals.

169 Discovery of CD8+ T Cell Epitopes Encoded by the HIV 5′ Leader Sequence

Edward Kreider[1]; Katja J. Pfafferott[2]; Thomas Partridge[2]; Hui Li[1]; Ranjit Warrier[1]; Benedikt M. Kessler[2]; Andrew J. McMichael[2]; Persephone Borrow[2]; Beatrice H. Hahn[1]; George M. Shaw[1]
[1]University of Pennsylvania, Philadelphia, PA, US; [2]University of Oxford, Headington, United Kingdom

Background: The HIV-1 5′ leader consists of the RNA upstream of canonical coding regions, encodes essential replicative functions, and exhibits the highest degree of conservation within the viral genome. We hypothesized that the 5′ leader, despite its designation as the 5′ "untranslated region," encodes previously uncharacterized open reading frames (ORFs) that are expressed from AUG-like start codons and harbor epitopes that are recognized by host T cell responses.

Methods: Single genome sequencing (SGS) was conducted on plasma virus from HIV-1-infected humans. Interferon-γ ELISPOT and intracellular cytokine staining were performed on PBMCs stimulated with autologous peptides or putative escape variants encoded by the 5′ leader sequence. Mass spectrometry analysis of major histocompatibility complex (MHC)-presented epitopes was conducted on peptides purified using MHC immunoprecipitation, acid elution, and reverse phase liquid chromatography of lysates from HIV-IIIB infected CD4+ T cells. Ribosomal profiling was used to identify AUG-like translation initiation sites.

Results: SGS of virus from HIV-1-infected humans demonstrated mutational patterns suggestive of virus escape throughout the 5′ leader. Based on these escape patterns, 4 potential ORFs were identified: one in the transactivation response element (TAR), one within U5, one surrounding the dimerization initiation signal (DIS), and one around the major splice donor. Screening for a T cell response to autologous transmitted/founder and putative escape peptides from these ORFs revealed CD8+ T cell recognition of an epitope within the DIS stem loop ORF. Mass spectrometry analysis of MHC-bound peptides from HIV-IIIB-infected T cells revealed presentation of two overlapping TAR peptides, LA14 and LL8. Ribosomal profiling demonstrated translation initiation at one-off AUGs within these two newly identified ORFs. Analysis of sequences in the Los Alamos HIV compendium showed that 91% of Group M viruses encode a DIS stem loop ORF and 93% of non-Clade A Group M viruses encode a TAR ORF.

Conclusions: We report here the discovery of multiple previously unrecognized ORFs in the HIV-1 5′ leader, or 5′ "untranslated region." Peptides from these ORFs are presented on infected CD4+ T cells and can target these cells for T cell recognition. The discovery of a novel source of T cell epitopes within such a highly conserved and functionally important region of the genome has implications for both vaccine development and immunopathogenesis research.

170LB Neutralizing Antibodies Differ Between HIV-1–Infected RV144 Vaccinees and Placebos

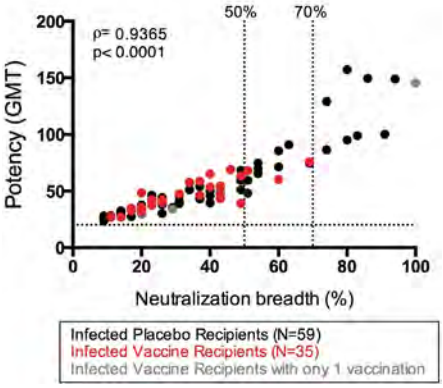
Shelly J. Krebs[1]; Morgane Rolland[1]; Sodsai Tovanabutra[1]; Ivelin Georgiev[2]; Agnes-Laurence Chenine[1]; Victoria R. Polonis[1]; Supachai Rerks-Ngarm[3]; Peter D. Kwong[2]; Nelson L. Michael[1]; Jerome H. Kim[1]
on behalf of the RV152 Study Group
[1]US Military HIV Research Program, Silver Spring, MD, US; [2]Vaccine Research Center, NIAID, NIH, Bethesda, MD, US; [3]Ministry of Public Health, Bangkok, Thailand

Background: Elucidating the ontogeny of broadly neutralizing antibodies (NAb) within infected individuals may identify important factors to consider in vaccine development. Although NAbs were not a correlate of risk in the RV144 HIV vaccine trial, B cell priming by vaccination may have accelerated the production of specific NAb lineages after infection. We asked if RV144 vaccine recipients who became infected elicited NAbs that varied in breadth, potency, and specificity compared to RV144 infected placebo recipients.

Methods: Samples from 94 infected RV144 individuals were evaluated for NAbs at 1-3 years post-diagnosis prior to the initiation of ART. Using a high-throughput robotic microneutralization assay, samples were analyzed against a panel of 35 viruses from subtypes A, B, C, D, CRF_01 AE, and CRF_02 AG. Included within this panel were 21 pseudoviruses where the pattern of neutralization can predict NAb specificity. Neutralization breadth, potency, and specificity of the responses observed after infection were compared between the vaccine and placebo recipients.

Results: Aggregate analysis revealed breadth and potency of neutralization were highly correlated (ρ= 0.94; p<0.001; Fig.1). Seventeen (29%) placebos while only 3 (10%) vaccine recipients neutralized >50% of the 35 virus panel (Fig.1). At three years post-diagnosis (956-1198 days), 8 placebo and 1 vaccine recipients neutralized >70% of the panel (Fisher's exact test, p=0.08), noting that the single vaccine recipient had only received 1 out of the 6 RV144 immunizations (Fig. 1). A trend toward increased breadth in the placebo group compared to the vaccine group (median= 40 vs 30, p=0.08) was also observed. The CD4 binding site and/or MPER were predicted as the dominant NAb specificities from both the placebo and vaccine groups, at 77% and 63% respectively.

Fig. 1: RV144 Neutralization



Conclusions: We report differences in neutralization breadth and potency between infected vaccine and placebo recipients of RV144. These data suggest a restriction in the vaccine group in the ability to produce broad NAb responses post-infection compared to the placebo group, raising the hypothesis that infected vaccinees define a group with intrinsically less effective HIV-1 immune responses. Further studies will provide a better understanding of the development of antibody responses in HIV-1 infected subjects, the potential role of vaccination on post-infection humoral responses, and the interrelationship between HIV-1 evolution and antibody responses.

Themed Discussion Abstracts

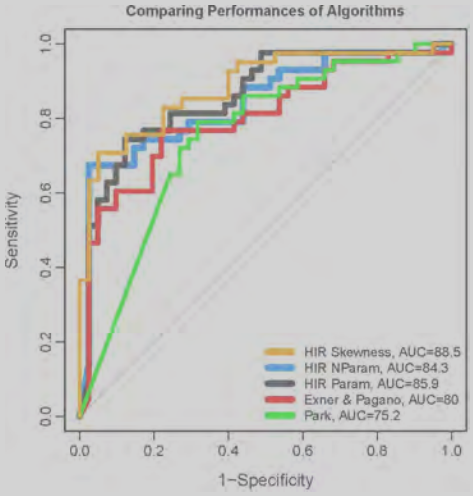
612 A Generalized Entropy Measure of Viral Diversity for Identifying Recent HIV-1 Infections

Julia W. Wu; Oscar Patterson-Lomba; Marcello Pagano
Harvard School of Public Health, Boston, MA, US

Background: There is a need for incidence assays that accurately estimate HIV incidence based on cross-sectional specimens. Viral diversity-based assays have shown promises but are not particularly accurate. We hypothesize that certain viral genetic segments are more predictive of recent infection than others and aim to improve assay accuracy by employing classification algorithms that focus on the highly informative regions (HIR).

Methods: We analyzed HIV *gag* sequences from a cohort in Botswana. Forty-two subjects newly infected by HIV-1 Subtype C were followed longitudinally through 500 days post-seroconversion. Using sliding window analysis, we screened for genetic segments within *gag* that best differentiate acute versus chronic infection. We used both non-parametric and parametric approaches to evaluate the discriminatory abilities of sequence segments. Segmented Shannon Entropy measures on HIRs were aggregated to develop generalized entropy measures to improve prediction of recency, defined as infection within past 6 months. With logistic regression as the basis for our classification algorithm, we evaluated the predictive power of these novel biomarkers and compared them with recently reported viral diversity measures using Area under the Curve (AUC) analysis. To further improve prediction, we also explored other diversity-related biomarkers.

Results: Change of diversity over time varied across different sequence segments within *gag*. The top 50% most informative segments were identified through non-parametric and parametric approaches. In both cases HIRs were in non-flanking regions and less likely in the *p24* coding region. These new indices outperformed previously reported viral-diversity-based biomarkers. Including skewness in the assay further improved the AUC (see Figure 1), whereas other existing methods did not add much additional predictive power. Sensitivity analysis suggests that antiretroviral use had little impact on our assay performances. We also demonstrate that sensitivity and specificity depend on the datasets used and the underlying distributions of time-since-infection. This explains why we obtained different AUC values compared to previous studies.



Comparing predictive performances of different algorithms.

Conclusions: Our generalized entropy measure of viral diversity demonstrates the potential for improving accuracy when identifying recent HIV-1 infections. We also show that to properly compare and evaluate assay performances, the distribution of time-since-infection in the validation dataset needs to be accounted for.

626 Viral Load is Critical in Limiting False-Recent Results From HIV Incidence Assays

Reshma Kassanjee[1]; Shelley Facente[2]; Sheila Keating[3]; Elaine McKinney[4]; Kara Marson[2]; Christopher D. Pilcher[2]; Michael Busch[3]; Gary Murphy[4]; **Alex Welte**[1]
The Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA)
[1]*South African DST/NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), University of Stellenbosch, Stellenbosch, South Africa;* [2]*University of California San Francisco, San Francisco, CA, US;* [3]*Blood Systems Research Institute, San Francisco, CA, US;* [4]*Public Health England, London, United Kingdom*

Background: The cross-sectional use of (biomarker) tests for recent HIV infection in principle offers affordable, low-bias options for incidence estimation. For currently available assays, viral suppression (due to elite control or antiretroviral treatment) is predictive of long-term infections being ('falsely') classified as 'recent'. Surveillance requires a not-too-transient 'mean duration of recent infection' (MDRI) – preferably at least 6 months. Assay readings below a chosen threshold are interpreted as indicating 'recent' infection, and any assay threshold sufficiently high to achieve a large MDRI inevitably incurs a substantial 'false-recent rate' (FRR), which should preferably be no higher than 1%. The performances of seven assays (BED, Limiting Antigen (LAg), Less-Sensitive (LS) Vitros, Vitros Avidity, BioRad Avidity, Architect Avidity, Geenius) were compared, in stand-alone form and in conjunction with a rule that low viral load is indicative of non-recent infection, allowing for varying assay and viral load thresholds.

Methods: Specimens were used from a growing repository, previously described, of over 6000 specimens representing over 2000 subjects from studies in Africa, Brazil and the United States. Assay thresholds were adapted to produce the same MDRI, estimated by binomial regression. Within a model scenario inspired by the contemporary South African context, the net model population-level FRRs were estimated by combining FRR estimates for key subgroups (stratifying by time since infection and treatment status).

Results: Table 1 shows the model population-level FRR for each assay, using an assay threshold that provides an MDRI of 200 days in each case, used either alone or with a viral load rule (using viral load thresholds of 75 and 1000 copies/ml).

Long-infected population	False-recent rate[1]								
	Treatment-naïve[2]			Treated and virally-suppressed			Treatment coverage of 30%		
Viral load threshold (copies/ml)	0	75	1000	0	75	1000	0	75	1000
Architect Avidity	3.9%	4.3%	4.7%	43.1%	0.0%	0.0%	15.7%	3.0%	3.3%
BED	2.1%	2.2%	2.7%	60.4%	0.0%	0.0%	19.6%	1.5%	1.9%
BioRad Avidity	0.8%	0.9%	1.0%	20.9%	0.0%	0.0%	6.8%	0.6%	0.7%
Geenius	3.9%	4.1%	4.4%	68.7%	0.0%	0.0%	23.4%	2.9%	3.1%
LAg	0.6%	0.5%	1.1%	60.5%	0.0%	0.0%	18.5%	0.4%	0.8%
LS-Vitros	4.3%	3.9%	3.3%	67.2%	0.0%	0.0%	23.1%	2.7%	2.3%
Vitros Avidity	3.3%	3.4%	3.3%	61.6%	0.0%	0.0%	20.8%	2.4%	2.3%

[1] For a choice of assay threshold that produces an MDRI estimate of 200 days; MDRI estimated using binomial regression (logit link with a cubic polynomial of time since infection as the predictor)

[2] Survival of treatment-naïve population follows a Weibull distribution with a mean of 10 years and standard deviation of 2.5 years; probability of 'recent' result analysed using binomial regression (described above)

Table 1: False-recent rates for recent infection testing algorithms

Conclusions: Adapted to provide a standard desirable MDRI of 200 days, none of the assays, used alone, provide an acceptably low FRR. With the use of any realistic viral load threshold, the FRR values drop dramatically, to between 0.4% and 3.3%, which is operationally feasible for population-level surveillance in high incidence contexts. Increasing the viral load threshold above 75 copies/ml offered little improvement in FRRs while decreasing MDRIs. Methods for optimally combining all information about predictors of 'false-recent' results into real-world context-specific FRR estimates require further development. Also, judicious combinations of these assays could potentially yield further improvements in performance.

625 False Recent Rates for Two Recent Infection Testing Algorithms, South Nyanza, Kenya

Clement Zeh[1]; David Maman[4]; Harrison Omondi[2]; Alex Morwabe[2]; Collins Odhiambo[2]; Beatrice Kirubi[4]; Irene Mukui[3]; Martinus W. Borgdorff[1]; Jean-François Etard[4]; Andrea A. Kim[1]

[1]US Centers for Disease Control and Prevention, Kisumu, Kenya; [2]Kenya Medical Research Institute, Kisumu, Kenya; [3]National AIDS and STI Control and Prevention, Nairobi, Kenya; [4]Médecins Sans Frontières, Paris, France

Background: Evaluation of candidate tests for recent HIV infection (TRI), designed to distinguish recent from chronic HIV infection, is an essential step prior to estimating cross-sectional HIV incidence. The TRI's false-recent rate (FRR), the probability that a chronic infection will misclassify as recent, is a required parameter for calculating HIV incidence and should not exceed 2% for accuracy. Because the FRR varies by TRI and sub-population, the FRR should be assessed in all settings in which HIV incidence will be estimated. We compare the FRR for the Limiting Antigen Avidity Enzyme Immunoassay (LAg) and Bio-Rad Avidity Enzyme Immunoassay (Bio-Rad), respectively, in a high HIV prevalence setting in South Nyanza, Kenya.

Methods: We conducted a population-based household survey of persons aged 15-59 years in Ndhiwa District in South Nyanza, Kenya. HIV treatment naive participants with documented chronic HIV infection (defined as testing HIV+ in the survey and reporting the first HIV+ test result ≥12 months preceding the survey) were tested for recent infection using the LAg and Bio-Rad on serologic blood samples. Recent infection was defined based on two recent infection testing algorithms (RITA): 1) a multi-assay algorithm (MAA) which defined a recent case as: a) tested recent on the TRI; b) not virally suppressed defined as HIV-1 RNA concentration ≥400 copies/mL; and 2) a single-assay algorithm (SAA) which defined a recent case as tested recent on the TRI. The FRR was calculated by dividing the number of recent cases observed on the RITA by the number of chronic infections tested.

Results: Of 1,465 HIV-positive samples, 835 (57.0%) were chronic infections. Based on the MAA, the FRR was 0.5% (95% CI 0.01 – 1.0) for LAg and 2.4% (95% CI 1.4 – 3.4) for Bio-Rad. Based on the SAA, the FRR was 4.6% (95% CI 3.2 – 6.0) for LAg and 7.2% (95% CI 5.5 – 9.0) for Biorad. The FRR did not differ by sex and RITA, but varied by age group for the two RITAs. In the MAA, the FRR was highest among youth aged 15-24 years (1.2%; 95% CI 0 – 3.5 for LAg; 3.5%; 95% CI 0 – 7.4 for Bio-Rad). In the SAA, the FRR was highest among persons aged 45-59 years at 5.7%; 95% CI 2.8 – 8.6 for LAg and 8.9%; 95% CI 5.4 – 12.5 for Bio-Rad.

Conclusions: The recommended threshold for a FRR was met by LAg, but only in the MAA which excluded individuals with suppressed viral load. Performance of the TRIs using the SAA resulted in high FRRs that are inappropriate for estimating incidence.

622 The Effect of HIV-1 Subtype A, C and D on Cross-Sectional Incidence Assay Performance

Andrew F. Longosz[2]; Mary Grabowski[2]; Charles S. Morrison[3]; Ronald H. Gray[2]; Connie Celum[4]; Quarraisha Abdool Karim[5]; Hilmarie Brand[6]; Thomas C. Quinn[1]; Susan H. Eshleman[2]; **Oliver B. Laeyendecker**[1]

[1]National Institute of Allergy and Infectious Diseases, Baltimore, MD, US; [2]Johns Hopkins University, Baltimore, MD, US; [3]FHI 360, Durham, NC, US; [4]University of Washington, Seattle, WA, US; [5]CAPRISA, University of KwaZulu-Natal, Congella, South Africa; [6]SACEMA, Stellenbosch University, Stellenbosch, South Africa

Background: We examined the impact of HIV subtype A, C and D on the performance of serologic cross-sectional HIV incidence assays.

Methods: Three assays were evaluated: the limiting antigen avidity enzyme immunoassay (LAg-Avidity assay), the BED capture enzyme immunoassay (BED-CEIA), and an avidity assay based on the Genetic Systems 1/2 + O ELISA (BioRad-Avidity assay). We evaluated 4,821 plasma and serum samples from individuals known to be infected with HIV-1 subtypes A, C and D from 6 different cohort studies in Zimbabwe, Uganda, South Africa, Kenya, Zambia and Botswana. This study included 2,045 subtype A samples (212 samples from the 2008-2009 Rakai Community Cohort Study (RCCS) and 1,833 samples from the Ugandan Genital Shedding (GS) Study. 1,697 subtype C samples (329 samples from the Ugandan and Zimbabwean GS Studies, 85 samples from HPTN 039, 727 samples from the Partners in Prevention Study and 556 samples from the CAPRISA 004 Trial Group) were analyzed. 1,079 subtype D samples (781 samples from the Ugandan Genital Shedding (GS) Study and 298 samples from the 2008-2009 RCCS) were tested. Date of HIV seroconversion was defined as either the midpoint between the last negative and first positive HIV antibody test, or fifteen days after acute infection was documented (defined as HIV RNA positive / HIV antibody negative). Viral load and HIV-1 subtype data were determined previously in parent studies. Mean duration of recent infection (MDRI) was calculated for subtypes A, C and D using a time window of two years post-seroconversion. To define recent infection, assay cutoffs of 1.5 normalized optical density (OD-n), 0.8 OD-n and 40% avidity index (AI), were used for the LAg-Avidity assay, BED-CEIA, and Bio-Rad-Avidity assay respectively. The false recent rate (FRR), the fraction of samples misclassified as recent, was calculated for all samples and those with detectable viral loads (>400 cps/ml).

Results: There were significant differences for MDRI and FRR estimates by subtype for all three assays (see Table). The largest differences in MDRI were seen for the LAg-Avidity and BED-CEIA assays between subtypes A and D. FRR results were significantly higher for subtype D for all three assays.

Table. Estimated test properties (95% confidence intervals) for each assay, by subtype

Recent/nonrecent threshold (unit)	Number of subjects (data points)	LAg-avidity 1.5 OD-n	BED 0.8 OD-n	BioRad avidity 40% AI
MDRI (days)[a]				
Subtype A	82 (577)	160.5 (144.6-175.7)	291.5 (278.0-303.6)	121.7 (111.7-132.8)
Subtype C	490 (1115)	127.9 (117.0-137.9)	204.9 (194.5-215.3)	138.0 (128.7-147.5)
Subtype D	30 (223)	204.6 (178.2-228.9)	281.0 (258.2-301.1)	150.6 (120.8-180.5)
FRR (%)				
Subtype A	290 (1468)	1.36 (0.83-2.09)	15.0 (13.2-17.0)	0.27 (0.07-0.70)
Subtype C	491 (582)	2.58 (1.44-4.22)	7.39 (5.40-9.82)	0.86 (0.28-1.99)
Subtype D	329 (856)	12.4 (10.3-14.8)	19.9 (17.2-22.7)	13.7 (11.4-16.2)
FRR (%) for VL+				
Subtype A	290 (1352)	0.52 (0.21-1.06)	13.3 (11.5-15.2)	0.30 (0.08-0.76)
Subtype C	451 (547)	2.38 (1.27-4.03)	6.95 (4.96-9.41)	0.73 (0.20-1.86)
Subtype D	328 (705)	6.24 (4.57-8.29)	13.6 (11.2-16.4)	13.8 (11.3-16.5)

AI, avidity; FRR false recent rate; LAg, limiting antigen avidity; MDRI mean duration of recent infection; OD-n, normalized optical density; VL+, viral load > 400 cps/ml;
[a]using a T = 2 years

Conclusions: The performance of each of the three assays varied by HIV subtype and subtype D had the highest false recent rates. These results highlight the need to optimize and validate testing algorithms for cross-sectional HIV incidence estimation in populations with the relevant HIV subtype distributions

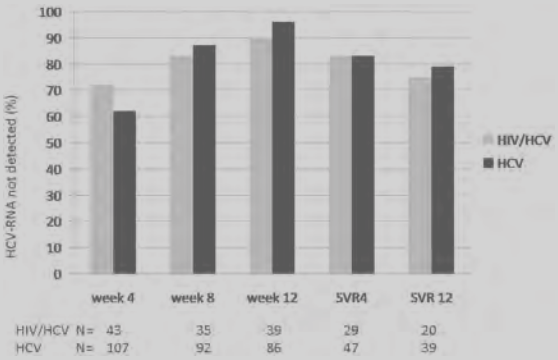
646 German Cohort on Sofosbuvir-Based Therapy for HIV/HCV and HCV Infection (GECOSO)

Stefan Christensen[2]; Ingiliz Patrick[3]; Dietrich Hueppe[7]; Thomas Lutz[4]; Karl Georg Simon[6]; Knud Schewe[5]; Heiner Busch[2]; Axel Baumgarten[3]; Guenther Schmutz[1]; **Stefan Mauss**[1]
[1]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; [2]CIM Infectious Diseases, Muenster, Germany; [3]Medizinisches Infektiologie Zentrum Berlin, Berlin, Germany; [4]Infektiologikum, Frankfurt, Germany; [5]Infektionsmedizinisches Centrum Hamburg, Hamburg, Germany; [6]Practice for Gastroenterology Leverkusen, Leverkusen, Germany; [7]Practice for Gastroenterology Herne, Herne, Germany

Background: Sofosbuvir (SOF) was approved in Europe in January 2014 with limited study data. In particular, interferon based triple therapy in HIV/HCV coinfection and pretreated patients were not systematically studied. Here, we present real-life data on SOF-based treatments from Germany.

Methods: In this multicenter cohort, all patients who were started on the following treatment regimens were documented: SOF/ribavirin (RBV), SOF/daclatasvir, SOF/simeprevir, and SOF/PegIFN/RBV. For the current analysis due to the limited observational period only patients treated with PegIFN/RBV/SOF were analysed. In February 2015 complete data sets for the first three therapy regimen will be available.

Results: Overall, 266 patients were enrolled so far. Of those, 193 were HCV-monoinfected and 73 HIV/HCV-coinfected. The genotype (GT) pattern was: GT1 n=156, GT2 n=17, GT3 n=68, GT4 n=24. Liver cirrhosis was present in 85/266 (32%) patients. Pretreated patients were 134/266 (50%). 161 (61%) patients were treated with SOF/PegIFN/RBV. The SVR12 rate overall was 78%.The viral response under therapy did not substantially differ between HIV/HCV coinfection and HCV-monoinfection (see figure). In addition SVR 4 and 12 were comparable. One patient showed a non-response (HCV) and one got re-infected under therapy with a different genotype (HIV/HCV). So far <5% of patients discontinued therapy prematurely or were lost to follow up.



Conclusions: In this preliminary analysis, response rates for HIV/HCV-coinfected and HCV-monoinfected patients treated with SOF/PegIFN/RBV were similar. The SVR12 rate seems to be lower than in the NEUTRINO study despite a low discontinuation rate. The lower SVR rate may be attributable to the cohort population containing more difficult-to-treat patients.

649 Successful HCV Treatment With Direct Acting Antivirals in HIV/HCV Patients

Jennifer L. Grant[1]; Valentina Stosor[1]; Frank J. Palella[1]; Richard M. Green[1]; Guajira Thomas[1]; Donna V. McGregor[1]; Milena M. McLaughlin[2]; Sudhir Penugonda[1]; Michael Angarone[1]; **Claudia Hawkins**[1]
[1]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [2]Midwestern University, Chicago, IL, US

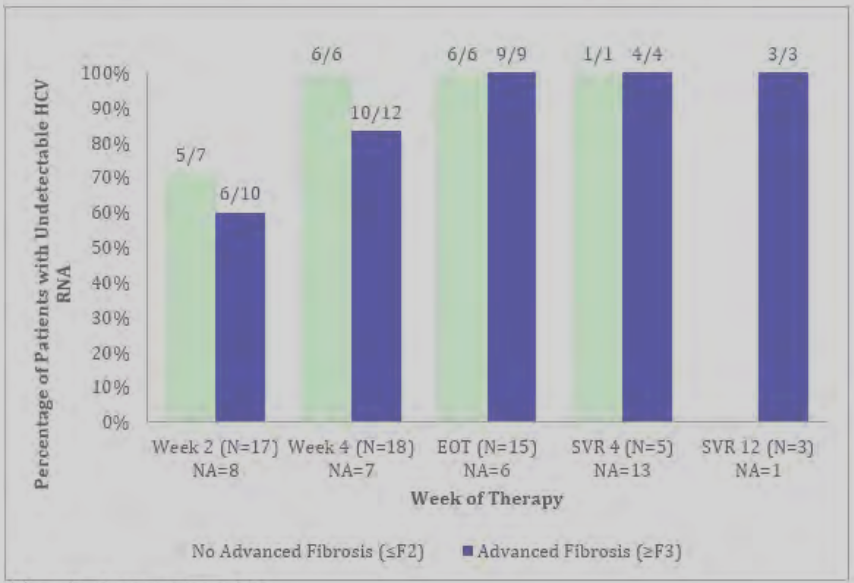
Background: IFN-free combinations of direct acting antivirals (DAA) are associated with high cure rates in HCV-infected patients. The SOF/SMV combination has not yet been studied in HIV/HCV co-infected persons. We evaluated outcomes in HIV/HCV patients receiving IFN-free DAA therapy in a large urban clinic in Chicago.

Methods: In a prospective observational analysis of HCV treatment experienced and treatment naïve co-infected adults (≥18 years) enrolled in the Northwestern University Viral Hepatitis Registry from Jan-Sep 2014, we evaluated the efficacy and safety of SOF/RBV (24 weeks) and SOF/SMV (12 weeks). HCV virologic responses were assessed at week 2 and then monthly during therapy (Rx) and 4 and 12 weeks after completion of Rx (SVR 4 and 12). HCV relapse was defined as a detectable HCV-RNA (lower limit of detection 15 IU/mL) at 4 or 12 weeks after Rx completion. We used chi-square and students' T-test (SPSS version 22.0, Armonk, NY; IBM Corp.) for between group comparisons.

Results: We evaluated 42 HIV/HCV patients [median age 53 years (IQR 47, 60); 81% male; 50% Caucasian; median CD4+ T cell count 522 cells/mm^3 (IQR 292, 660)] for HCV Rx. Risk factors for HCV included MSM (41%) and IDU (41%). Rx was initiated in 32/42 (76%) patients with either SOF/SMV (28, 87.5%) or SOF/RBV (4, 12.5%). Males (85.3% vs. 25% (females); p<0.01) and patients with higher mean FibroSure™ scores (0.70 vs. 0.46; p=0.047) were more likely to receive HCV Rx. There were 21 (66%) with genotype (GT) 1a, 8 (25%) with GT 1b, and 1 each (3%) with GT 2, 3 and undifferentiated. 14/32 (44%) had previously received either PEG/RBV (12/14) or PEG/RBV+BOC (2/14). Median pre-Rx HCV-RNA was 1,384,532 copies/ml (IQR 798,853, 3,772,827) and 23/32 (72%) had advanced liver fibrosis (≥F3). All patients received indicated ART. HCV-RNA responses are shown in Figure

1. No HCV relapses have occurred to date in patients receiving either DAA Rx. Minor adverse effects occurred in 14/29 (48%) patients, none of which resulted in HCV therapy discontinuation (pruritus, 17%, fatigue, 14%, grade 3 total bilirubin elevation, 10%). One death occurred unrelated to HCV Rx.

Figure 1.
HCV Virologic Outcomes in HIV/HCV Patients Receiving SOF/SMV



*All p-values for comparisons >0.05
**NA=lab data not available

Conclusions: In this non-clinical trial-based study of difficult to treat HIV/HCV-infected patients, use of SOF/SMV or SOF/RBV achieved rapid HCV-RNA declines and was well tolerated. HIV co-infection should not be considered a barrier to successful HCV treatment using these combinations. Accrual and treatment of patients is ongoing.

645 Effectiveness of Sofosbuvir/Simeprevir for HIV/HCV Patients in Clinical Practice

Jody Gilmore[1]; Kenneth Lynn[1]; Delisha Breen[1]; Stacey Trooskin[2]; Jihad Slim[3]; Nancy Scangarello[3]; Alvin Kingcade[4]; Katie Hunyh[4]; Vincent Lo Re[1]; **Jay R. Kostman**[1]

[1]Perelman School of Medicine, Philadelphia, PA, US; [2]Drexel University College of Medicine, Philadelphia, PA, US; [3]St Michael's Medical Center, Newark, NJ, US; [4]Philadelphia Health Management Corporation, Philadelphia, PA, US

Background: HIV/HCV-coinfected patients have been underrepresented in clinical trials of all-oral therapies for chronic HCV genotype 1 infection. Our objective was to assess virologic responses and tolerability of sofosbuvir + simeprevir (sof/sim) in HIV/HCV-coinfected patients compared to those with HCV alone.

Methods: We performed a cohort study among HCV-infected patients treated with sof/sim at 4 community-based and academic centers. The main outcome was end-of-treatment (EOT) HCV virologic response. HCV RNA, liver aminotransferases, and sof/sim discontinuations were evaluated over 12 weeks of treatment and 12 weeks of follow-up. Results were stratified by HIV status and by the presence of advanced hepatic fibrosis/cirrhosis.

Results: Eighty-one patients (37 coinfected; 44 monoinfected) were treated with sof/sim between 12/2013 and 9/2014. Fifty-nine percent were African American, 61% were male, 73% had METAVIR stage 3/4 fibrosis, and 46% had prior HCV therapy (49% null or partial responders; 16% relapsers; 35% stopped due to toxicity). The most common HIV regimens in coinfected persons included raltegravir, dolutegravir, or rilpivirine with either tenofovir/emtrictabine or abacavir/lamivudine. Among HIV/HCV patients, 54% and 87% achieved an HCV RNA that was not quantifiable at 2 and 4 weeks of therapy, respectively, compared to 55% and 81% for HCV-monoinfected patients ($p>0.5$). Those with METAVIR stage 3/4 were equally likely to achieve HCV suppression by 4 weeks compared to those with less fibrosis regardless of HIV status (61% vs. 67% in coinfected patients, $p=0.68$; 56% vs. 75% in monoinfected patients, $p=0.33$). Overall, mean levels of alanine aminotransferase decreased from 54 U/L to 22 U/L within 2 weeks of sof/sim initiation. Of the 81 patients, only 5 (6%; 3 coinfected; 2 monoinfected) prematurely discontinued therapy (1 due to nonresponse; 1 for cutaneous reaction; 3 lost to follow-up). Among 42 patients completing 12 weeks of therapy, 37 (88%) achieved an EOT response (89% in coinfected patients; 88% in monoinfected patients, $p>0.5$). At the time of this analysis, 22 patients were followed for at least 4 weeks after the completion of therapy with 2 virologic relapses in monoinfected patients, 1 with METAVIR stage 3/4.

Conclusions: An all-oral sof/sim regimen was effective for patients with chronic HCV genotype 1, regardless of HIV status, previous treatment response, and stage of fibrosis. Adverse events were rare, even in patients with advanced fibrosis/cirrhosis.

648 Simeprevir and Sofosbuvir Regimens for Hepatitis C: Decompensation and Serious AEs

Ponni V. Perumalswami[1]; Kian Bichoupan[1]; Lawrence Ku[1]; Neal M. Patel[1]; Rachana Yalamanchili[1]; Thomas Schiano[1]; Mark Woodward[2]; Douglas Dieterich[1]; Andrea D. Branch[1]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, US; [2]George Institute for Health at the University of Oxford, Oxford, United Kingdom

Background: New therapies for hepatitis C virus (HCV) were well-tolerated in registration trials; however, results in real world clinical practice can be different. We characterized hepatic decompensation and serious adverse events (SAEs) in patients receiving standard care at the Mount Sinai Medical Center.

Methods: All HCV infected patients treated with regimens that contained sofosbuvir (SOF) and/or simeprevir (SMV) were included. The Cases experienced at least one of the following: hepatic decompensation, indicated by new or increased jaundice, ascites, encephalopathy, or sepsis, or another SAE. There were two cohorts: Cohort 1 included 466 patients, Cohort 2 included 43 liver transplant (LT) patients. The incidence of decompensation/SAE was calculated for each cohort. Within each cohort, a matched Case-Control study was performed to identify risk factors for decompensation/SAE. For Cohort 1, up to five Controls were selected for each Case based on treatment regimen and duration. For Cohort 2, matching was 1:2. Cases and Controls were compared using matched conditional exact analysis.

Results: A total of 489 patients met the inclusion criteria: 466 in Cohort 1 (non-LT) and 43 in Cohort 2 (LT). There were 13 non-LT Cases (2.8%) and 8 LT Cases (19%), $p< 0.01$ for the comparison. In Cohort 1, most (62%) were on SOF/RBV, 15% were on SOF/PEG/RBV, and 23% were on SMV/SOF. Among 67 non-LT patients on PEG/RBV-free regimens, three

decompensated/experienced an SAE (4%). In Cohort 2, all were on SOF/RBV. Treatment was discontinued in 4/13 (31%) of non-LT Cases and in 2/8 (25%) of LT Cases. Similar to registration trials, liver decompensation/SAE lead to treatment discontinuation in 1% (5/466) of the entire non-LT Cohort and in 5% (2/43) of the entire LT Cohort. Among non-LT patients, risk factors for SAE/decompensation included low baseline albumin, high INR, and high total bilirubin. In LT patients, lower hemoglobin, eGFR, ALT, AFP and higher serum creatinine were risk factors for SAE/decompensation.

Conclusions: This study identified subgroups of non-LT and LT patients who may require more intensive monitoring and additional interventions to successfully complete SMV- and SOF-based treatment regimens. Patients with reduced hepatic biosynthetic function and LT patients were especially vulnerable to serious AEs and decompensation (DA031095, DK090317).

651 Majority of HIV/HCV Patients Need to Switch ART to Accommodate Simeprevir

Rebecca Cope[1]; Aaron Pickering[2]; Thomas Glowa[1]; Samantha Faulds[1]; Peter Veldkamp[1]; **Ramakrishna Prasad**[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]University of Maryland, Glen Burnie, MD, US

Background: The impact of drug-drug interactions (DDIs) between Simeprevir (SMV) and antiretrovirals (ART) in limiting HCV treatment among HIV/HCV co-infected individuals in clinical practice settings is unknown. We determined: a) the need to switch antiretroviral therapy (ART) prior to initiation of SMV; and b) the feasibility of switching ART to allow SMV use. We hypothesized that the majority of co-infected patients will require an ART switch and a safe and effective ART switch will be challenging in patients on a protease inhibitor (PI) based ART regimen.

Methods: A retrospective chart review was conducted at the University of Pittsburgh Medical Center's HIV/AIDS Program from June-August 2014. All patients with HIV and chronic HCV with a visit in the past 18 months were included. After collection of baseline characteristics, significant interactions between SMV and ART were identified based on available literature. If DDIs limited use of SMV, previous HIV genotype reports were reviewed to determine the feasibility of a safe and effective ART switch.

Results: Of 133 patients, 71% were male, 54% African American, 23% met criteria for advanced liver disease, 86% had HCV genotype 1, and 94% were currently on ART. The distribution of regimens was: ritonavir-boosted PI (PI/r) (38%); efavirenz (34%); raltegravir (11%); rilpivirine (6%); elvitegravir/cobicistat (1%); and other regimens including dolutegravir (4%). An ART switch to allow use of SMV was required in 103 (77%), most frequently for patients on efavirenz or a PI/r. For 47 (46%), a straightforward substitution could be made. For the remaining patients, a switch following HIV expert opinion was viable in 40 (39%), but no switch was possible in 16 (15%) due to archived HIV drug resistance mutations. Notably, for more than 30% of patients on a PI, an ART switch was not feasible.

Conclusions: The majority of HIV/HCV co-infected patients will require ART switch prior to use of SMV. Additionally, for nearly a third of patients on a PI, an ART switch may not be feasible. These findings are significant to real world clinical practice settings and highlight the complexity of using Interferon-free DAAs in this population and add further stress to an already burdened HIV care delivery system.

644 Sofosubuvir, Simeprevir, +/- Ribavirin in HCV Protease Inhibitor-Experienced Patients

Kristen M. Marks; Ethan M. Weinberg; Sonal Kumar; Carrie Down; Ype P. de Jong; Leah A. Burke; Mary C. Olson; Ira M. Jacobson

Weill Cornell Medical College, New York, NY, US

Background: Little data exists on use of HCV protease inhibitors (PIs) as part of a treatment (Rx) regimen for PI-experienced G1 patients (pts). Since polymorphisms associated with PI-resistance decrease to baseline levels over time in most studied subjects, sofosbuvir (SOF) + simeprevir (SMV) +/- ribavirin (RBV) represents a *potential* retreatment option for PI-experienced pts.

Methods: We compiled a retrospective cohort of HCV PI-experienced G1 pts treated with SOF+SMV+/-RBV at our center. Baseline factors including prior regimen & Rx response, fibrosis stage, HCV genotype & resistance testing (population-based) data, viral RNA levels, demographic data as well as on Rx response, SVR4, and SVR12 were collected and reported.

Results: In 2014, 15 pts with genotype 1 and prior PI experience initiated Rx because of clinical need with 12 wks SOF+SMV with (10) or without (5) RBV . Median age was 61 yrs (range 26-73), baseline HCV RNA 6.5 log IU/ml (5.5-7.0 log), 12 were male, and 10 had cirrhosis. PI Rx occurred 26 (5-85) months prior and included telaprevir (10), boceprevir (3), ABT 450/r (1), GS9451 (1) as part of Rx regimen with 11 nonresponders, 1 relapser, and 3 intolerant of Rx. All had genotype and resistance testing performed prior to SOF+SMV+/-RBV. Of the 9 G1a pts, Q80K was detected in 4, Q80L in1. Of the 6 G1b pts, V36I and T54S were detected in 1 pt each. No other mutations associated with PI resistance were detected.

Responses to SOF+SMV+/-RBV are shown in the table.

	Wk 4 on Rx	End of Rx	Wk 4 post Rx (SVR 4)	Wk 12 post Rx (SVR12)
# completing time point	15	15	14 (1 pending)	13 (2 pending)
# (%) suppressed below quantification (<15 or <43 IU/ml)	15 (100%)	15 (100%)	13 (93%)	12 (92%)
# (%) suppressed below detection	9 (56%)	15 (100%)	13 (93%)	12 (92%)
# relapse (%)			1* (7%)	1* (8%)

*The pt with relapse received SOF+SMV+RBV, had G1b, cirrhosis and a prior history of telaprevir-based Rx completed 14 months prior, and had no known mutations associated with resistance.

Conclusions: Conclusion: SOF+SMV+/-RBV treatment may be appropriate for carefully selected PI-experienced G1 pts including those with cirrhosis. Further study is needed to confirm these findings.

746 Cumulative HIV Care Measures Highly Associated With Acute Myocardial Infarction

Jorge L. Salinas[1]; Christopher T. Rentsch[2]; Vincent C. Marconi[1]; Janet Tate[3]; Adeel A. Butt[4]; Matthew S. Freiberg[4]; Matthew B. Goetz[5]; Maria Rodriguez-Barradas[6]; Amy Justice[3]; David Rimland[1]

[1]Emory University, Atlanta, GA, US; [2]Atlanta VA Hospital, Decatur, GA, US; [3]Yale University, New Haven, CT, US; [4]University of Pittsburgh, Pittsburgh, PA, US; [5]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US; [6]Baylor College of Medicine, Houston, TX, US

Background: After accounting for established risk factors, people living with HIV (PLWHIV) have a 50-75% greater risk of acute myocardial infarction (AMI) than uninfected individuals. Several underlying causes for this association have been suggested including ongoing chronic inflammation, immune suppression, and a greater burden of anemia, renal disease, liver disease, and hepatitis C infection. While many of these factors have been studied in a cross-sectional manner, few have considered the association of cumulative HIV care measures with AMI among PLWHIV. We hypothesized that measuring these factors in a cumulative way would be associated with AMI incidence.

Methods: Retrospective cohort study including PLWHIV starting antiretroviral therapy (ART) in the Veterans Aging Cohort Study Virtual Cohort (VACS VC) from 2000-2009. The impact of baseline, time-updated and cumulative measures of HIV viremia, CD4 count and the VACS Index were modeled. Cumulative measures were captured starting 6 months after ART initiation until AMI event, death, last clinic visit or censor date (December 31, 2009) and calculated as follows:

1) Copy Years viremia (CYV)= Area under the curve of HIV viral load (VL) measures.

2) CD4 Years (CD4Y)= Area under the curve of CD4 measures.

3) VACS Index years (VISY)= Area under the VACS Index curve.

Areas under the curve were calculated using the trapezoidal rule. The VACS Index score was calculated using age, HIV-1 RNA, CD4, aspartate and alanine transaminases, hemoglobin, platelet count, creatinine and known hepatitis C infection. An online calculator is available (http://vacs.med.yale.edu). The primary outcome was incident AMI determined using Medicare and VA ICD9 codes. Multi-variable proportional hazard (PH) models were fit for time to AMI.

Results: 12,131 patients were included in the analysis. Separate PH models were fit for different measures of VL, CD4 and the VACS Index (basal, time-updated and cumulative) and results are presented in table 1. While all three cumulative measures predicted the studied outcome, VCY≥63, 000 copy-years/mL (HR=4.17; 95%CI=3.59-4.85) and CD4Y<750 cell-years/mm^3 (HR=5.61; 95%CI=4.56-6.90); patients with higher VACS Index score-years had the highest risk of AMI (VISY≥250; HR=40.56; 95%CI=33.25-49.47).

HIV viral load measures				CD4 measures				VACS Index measures			
	Person-years	AMIs	Adjusted HR*		Person-years	AMIs	Adjusted HR**		Person-years	AMIs	Unadjusted HR***
Baseline VL (copies/mL)				Baseline CD4 (cells/ mm^3)				Baseline VACS Index score			
<75,000	23,301	84	1	<200	22,582	80	1.45 (1.30-1.61)	<50	25,827	77	1
75,000+	23,749	84	1.12 (1.01-1.24)	200+	24,581	87	1	50+	15,888	68	2.79 (2.51-3.10)
Time-updated VL (copies/mL)				Time-updated CD4 (cells/mm^3)				Time-updated VACS Index score			
<500	47,957	156	1	<200	8,710	43	7.31 (6.29-8.49)	<25	26,830	59	1
500-4,199	2,586	8	1.85 (1.53-2.24)	200-349	9,587	45	2.20 (1.85-2.62)	25-39	13,037	50	2.43 (2.01-2.94)
4,200-38,999	2,783	18	2.85 (2.42-3.36)	350-499	11,120	39	1.42 (1.17-1.73)	40-59	8,857	47	6.78 (5.72-8.03)
39,000+	3,678	13	5.12 (4.52-5.8)	500+	27,362	69	1	60+	7,898	45	35.20 (30.31-40.88)
Time-updated viremia (VCY) (copy-years/mL)				Time-updated CD4-years (CD4Y) (cell-years/ mm^3)				Time-updated VACS Index score-years (VISY)			
<1,200	6,325	49	1	<750	4,608	45	5.61 (4.56-6.90)	<75	10,518	55	1
1,200-2,999	17,690	51	1.25 (1.02-1.54)	750-1,749	9,632	58	2.27 (1.86-2.77)	75-149	11,536	58	5.91 (5.04-6.94)
3,000-62,999	16,172	47	1.97 (1.67-2.32)	1,750-2,999	12,968	41	1.50 (1.22-1.84)	150-249	13,641	42	14.87 (12.37-17.88)
63,000+	16,818	48	4.17 (3.59-4.85)	3,000+	29,569	52	1	250+	20,362	46	40.56 (33.25-49.47)
Abbreviations: AMI: Acute myocardial infarction; HR: Hazard ratio; VL: Viral load; VCY: Viremia copy-years; VACS: Veterans Aging Cohort Study											
*Adjusted for age and baseline CD4 count **Adjusted for age and baseline HIV viral load ***The VACS Index includes age, VL, CD4, aspartate and alanine transaminases (AST, ALT), hemoglobin, platelets, creatinine and hepatitis C infection											

Table 1. Multivariable Cox Proportional Hazards analyses of factors associated with time to Acute Myocardial Infarction among patients starting Initial ART regimens in the VACS Virtual Cohort; 2000-2009.

Conclusions: Cumulative measures of viral load, CD4 count and VACS Index provide added information about risk of AMI, of these, VACS Index is the most comprehensive.

747 Cardiovascular Disease Risk Prediction in the HIV Outpatient Study (HOPS)

Angela M. Thompson-Paul[1]; **Kenneth A. Lichtenstein**[2]; Carl Armon[3]; Kate Buchacz[1]; Rachel Debes[3]; Joan S. Chmiel[4]; Frank J. Palella[4]; Stanley C. Wei[1]; Jacek Skarbinski[1]; John T. Brooks[1]

[1]US Centers for Disease Control and Prevention, Atlanta, GA, US; [2]National Jewish Health, Denver, CO, US; [3]Cerner Corporation, Vienna, VA, US; [4]Northwestern University, Feinberg School of Medicine, Chicago, IL, US

Background: HIV infection is associated with an increased risk of cardiovascular disease (CVD); however, it is unknown if commonly used CVD risk prediction tools accurately predict risk in HIV-infected persons. In this analysis, we examined four CVD risk prediction equations to determine if they accurately estimate events and predict risk events in a large diverse cohort of HIV-infected adults in the United States.

Methods: We analyzed longitudinal data on HIV Outpatient Study (HOPS) participants in care at 10 U.S. clinic sites as of 30 September 2013 who met the following criteria: had at least one year of follow-up after 1 January 2002, enrolled in the HOPS no later than 1 October 2010, had at least one total cholesterol measurement, and at least two systolic blood pressure measurements at baseline. We applied four CVD risk equations to the HOPS data to estimate 10-year CVD risk, and using Harrell's *C*-statistic assessed their predictive ability to discriminate patients who did vs. did not experience incident CVD events. Incident CVD events were defined for each risk equation are as follows: 1) Framingham Point Score (FPS)– myocardial infarction (MI), fatal coronary heart disease (CHD), stroke; 2) Pooled Cohort Equation (PCE) - MI, stroke, coronary artery disease (CAD); 3) Systematic COronary Risk Evaluation (SCORE) for low-risk populations – fatal MI, stroke, peripheral vascular disease, CAD; and 4) the Data Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study equations - MI, sudden death, CAD, stroke, and death from other CHD.

Results: There were 2392 participants with a median age of 43 years; 76% were male, 50% were non-Hispanic white, and 87% were antiretroviral experienced at baseline. Common co-morbid conditions included hypertension (50%), diabetes (10%), and high cholesterol (17%). In this cohort, 204 incident CVD events occurred during a median follow-up time of 6.5 years. All equations underestimated 10-year CVD risk to a variable degree (Table 1). The FPS, PCE, and D:A:D equations showed moderate discrimination (C-statistic range, 0.68 to 0.72), whereas SCORE showed poor discrimination (C-statistic=0.59).

HOPS participants (n=2,392)	10-Year CVD Risk Estimation			
	FPS	PCE	SCORE	D:A:D
C-statistic*	0.71	0.71	0.57	0.72
Expected events (E)	126	147	19	193
Observed events (O)	149	178	23	256
Ratio E/O	0.85	0.83	0.83	0.75
p-value	0.002	<0.001	0.02	<0.001
Abbreviations: FPS, Framingham Point Score; PCE, Pooled Cohort Equation; SCORE, Systematic COronary Risk Evaluation; D:A:D, Data Collection on Adverse Effects of Anti-HIV Drugs. * Harrell's C-statistic assessed the ability of each prediction model to discriminate patients who did vs. did not experience incident CVD events.				

Comparison of 10-year cardiovascular disease (CVD) risk estimation and discrimination in four CVD risk calculators in HIV-infected adults from the HIV Outpatient Study (HOPS).

Conclusions: The four risk prediction equations underestimated the 10-year risk of CVD in our large, diverse cohort of HIV-infected adults. To better estimate CVD risk in HIV-infected persons in the U.S., additional risk factors, such as immunologic or virologic status may need to be considered.

748 Incidence and Risk of Myocardial Infarction (MI) by Type in the NA-ACCORD

Daniel R. Drozd[1]; Mari M. Kitahata[1]; Keri N. Althoff[2]; Jinbing Zhang[2]; Susan R. Heckbert[1]; Matthew J. Budoff[3]; Frank J. Palella[4]; Daniel B. Klein[5]; Richard D. Moore[6]; Heidi M. Crane[1]

[1]University of Washington, Seattle, WA, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]University of California Los Angeles, Los Angeles, CA, US; [4]Northwestern University, Chicago, IL, US; [5]Kaiser Permanente Northern California, Hayward, CA, US; [6]Johns Hopkins University, Baltimore, MD, US

Background: HIV-infected persons may be at increased risk for cardiovascular disease (CVD) and MI, but the role of HIV in the pathogenesis of MI is unclear. The Universal Definition of MI (UDMI) classifies MIs by underlying pathophysiology into classic *primary* (type 1) MIs due to atherothrombotic coronary plaque rupture and *secondary* (type 2) MIs resulting from supply-demand mismatch caused by a heterogeneous set of clinical conditions including sepsis and cocaine-induced vasospasm. In the general population, primary MIs are more common than secondary MIs. Prior studies in HIV have not classified the type of MI and therefore, have examined primary and secondary MIs as a single endpoint, which may limit their ability to define the contribution of HIV to CVD and primary MI risk. We determined the incidence of adjudicated primary MIs distinct from secondary MIs and examined baseline risk factors for primary MIs.

Methods: MIs were centrally adjudicated in 7 NA-ACCORD clinical cohorts between 1996-2010 in patients who screened positive and classified according to the UDMI; primary events included invasive cardiac interventions (CABG, stent placement). Incidence rates (IRs) per 1,000 person-years (PY), adjusted incidence rate ratios (aIRRs), and 95% confidence intervals ([,]) were estimated using Poisson regression adjusted at baseline for sex, race/ethnicity, HIV risk group, year of enrollment, cohort, ever smoked, hypertension (HTN), diabetes (DM), dyslipidemia, chronic kidney disease (CKD), CD4 count, and HIV RNA (viral load); age was time-updated.

Results: There were 24,919 patients who experienced 262 primary and 205 secondary MIs in 95,728 PYs of follow-up: primary MI IR=2.74 [2.42, 3.09] and secondary MI IR=2.14 [1.87, 2.46]. Significant predictors of primary MI included age, HTN, DM, dyslipidemia, smoking, stage 4/5 CKD, and CD4 count (Table 1). Sepsis (33%), cocaine (8%), respiratory failure (5%), and hypertensive emergency (4%) combined accounted for 50% of all secondary MIs.

Table 1. Adjusted rate ratios (aIRR) and 95% confidence intervals for primary MI

	aIRR [95% CI]
Age	
<40	1.00
40-49	**3.42 [2.06, 5.68]**
50-59	**5.14 [3.05, 8.66]**
60-69	**9.96 [5.66, 17.53]**
Hypertension	**1.92 [1.45, 2.55]**
Diabetes mellitus	**2.01 [1.39, 2.89]**
Ever smoker	**2.02 [1.38, 2.94]**
Dyslipidemia	**1.75 [1.32, 2.32]**
Stage 4/5 CKD	**7.73 [3.05, 19.59]**
CD4 (cells/mL)	
<200	1.00
200-349	**0.63 [0.44, 0.90]**
≥350	**0.66 [0.49, 0.88]**
HIV viral load (copies/mL)	
<200	1.00
201-9,999	1.23 [0.88, 1.71]
10,000-99,999	**1.54 [1.06, 2.24]**
≥100,000	1.17 [0.71, 1.92]

Conclusions: Traditional CVD risk factors and immunosuppression significantly predict primary MIs. The high rate of secondary MIs emphasizes the need for greater clarity in outcome ascertainment in studies seeking to study the pathogenic role of HIV in CVD. Future analyses will examine the complex longitudinal relationship between primary MIs and HIV-specific factors including CD4 count, viral load, and ART.

750 HIV-Infected Veterans and the New ACC/AHA Cholesterol Guidelines: Got Statins?

Meredith E. Clement[1]; Lawrence Park[1]; Ann Marie Navar-Boggan[1]; Nwora L. Okeke[1]; Michael Pencina[1]; Pamela Douglas[1]; Susanna Naggie[1]

[1]Duke University, Durham, NC, US; [2]Duke University, Durham, NC, US; [3]Duke University, Durham, NC, US

Background: Cardiovascular disease, an HIV-associated non-AIDS related (HANA) condition, is an emerging threat to people living with HIV; thus, appropriate primary and secondary prevention is critical. In November 2013 updated guidelines for cholesterol treatment from the American College of Cardiology and the American Heart Association (ACC/AHA) substantially expanded recommendations for statin use among the general population for cardiovascular disease (CVD) prevention compared to the prior Adult Treatment Panel (ATP-III) guidelines. How these new recommendations impact adults with HIV-infection is unknown.

Methods: We used the Veterans Affairs (VA) Clinical Case Registry (CCR), one of the largest clinical databases of HIV-infected patients worldwide, to determine the impact of the new the new cholesterol guidelines on statin recommendations for HIV-infected veterans. Electronically available laboratory, medication, and comorbidity data from 2008 to 2010 were used to assess statin recommendations under the ATP-III and the 2013 AHA/ACC guidelines among male patients aged 40 to 75 years. Descriptive statistics are presented comparing the proportion of adults recommended under each guideline.

Results: 13293 male veterans with HIV-infection met inclusion criteria for the analysis. The average age was 54.6 years. Cardiovascular disease was present in 8.2% and diabetes in 15.4%. Of 13293 veterans, 5185 (39.0%) had been prescribed statin therapy (32.2% for primary prevention and 6.8% for secondary prevention). Overall, 11.6% of adults not previously eligible for statin therapy under ATP-III were newly recommended under ACC/AHA guidelines, with 7085 (53.3%) veterans recommended for statin therapy under the ATP-III guidelines compared to 8630 (64.9%) under the ACC/AHA guidelines. The majority of the increase in statin eligibility was in adults recommended for primary prevention; with 9.1% newly recommended based on 10-year risk score, 1.7% newly recommended based on diabetes, and 0.8% newly recommended based on presence of CVD.

	ATP-III	ACC/AHA
Already on Statin		
Primary prevention	4286 (32.2%)	4286 (32.2%)
Secondary prevention (CVD)	899 (6.8%)	899 (6.8%)
Subtotal	**5185 (39.0%)**	**5185 (39.0%)**
New Statin Recommended		
Primary prevention	1803 (13.5%)	3244 (24.4%)
LDL>190	70 (0.5%)	70 (0.5%)
Diabetes	248 (1.9%)	475 (3.6%)
10-yr Risk Score	1485 (11.2%)	2699 (20.3%)
Secondary Prevention (CVD)	97 (0.7%)	201 (1.5%)
Subtotal	**1900 (14.3%)**	**3445 (25.9%)**
No Statin Recommended		
Primary prevention	6104 (45.9%)	4663 (35.1%)
Diabetes	384 (2.9%)	157 (1.2%)
10-yr Risk Score	5720 (43.0%)	4506 (33.9%)
Secondary Prevention	104 (0.8%)	0
Subtotal	**6208 (46.7%)**	**4663 (35.1%)**
Total	**13293 (100%)**	**13293 (100%)**

Conclusions: In our study population of HIV-infected veterans, application of the new ACC/AHA cholesterol guidelines resulted in an approximate 12% absolute increase in the proportion of patients for whom statin therapy is indicated. The increased recommended use of statins is primarily related to risk assessed by the 10-year risk score of cardiovascular disease. It will be important to assess the benefit of this expanded prevention measure prospectively.

751 Evaluation of the ACC/AHA CVD Risk Prediction Algorithm Among HIV-Infected Patients

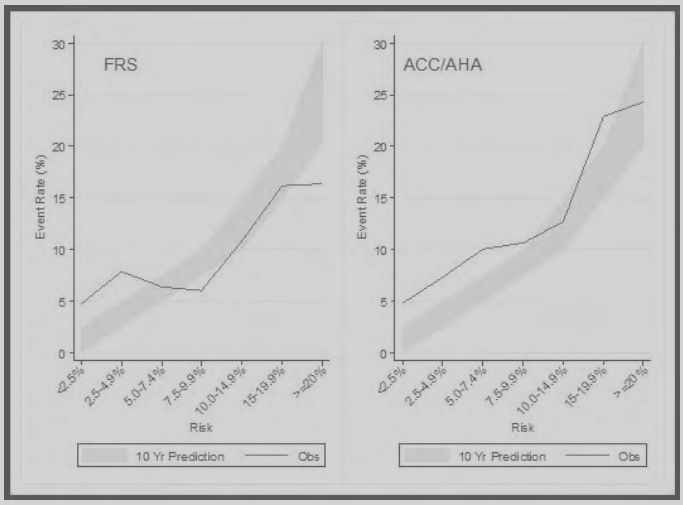
Susan Regan[2]; James B. Meigs[2]; Joseph Massaro[3]; Ralph B. D'Agostino[3]; Steven Grinspoon[2]; **Virginia A. Triant**[2]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Boston University, Boston, MA, US; [4]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

Background: The 2013 American College of Cardiology (ACC)/ American Heart Association (AHA) cardiovascular disease (CVD) risk prediction algorithm (Pooled Cohorts Equations) has not previously been evaluated in HIV populations.

Methods: Framingham Risk Scores (FRS) and ACC/AHA risk scores were calculated for patients in a longitudinal HIV clinical care cohort during a 3-year interval ending January 1, 2009. Patients were not eligible if they were under age 18, had expired prior to January 1, 2009, were missing relevant data to populate the risk score, or had undergone a relevant outcome event prior to the date of risk score calculation. CVD risk was considered high if 10-year predicted risk of the relevant outcome event was ≥10 percent for FRS and ≥7.5 percent for ACC/AHA. Outcome events were coronary heart disease (CHD) for FRS and atherosclerotic CVD (ASCVD) for ACC/AHA.

Results: The FRS was calculated for 2270 patients, with a median follow-up time of 6.3 years, and the ACC/AHA risk score was calculated for 2152 patients, with a median follow-up time of 6.2 years. Risk scores were discordant in 17 percent of patients, with the ACC/AHA score only predicting high risk in 10 percent and the FRS only predicting high risk in 7 percent. In comparisons of these discordant subgroups, patients classified as high-risk by ACC/AHA but low-risk by FRS were older (median age 56 for ACC/AHA high vs. 48 for FRS high) and more likely to be female (68% vs. 0%), diabetic (52% vs. 6%) and black (22% vs. 12%) but less likely to be smokers (44% vs. 66%) than those low-risk by ACC/AHA and high-risk by FRS. Actual event rates were estimated and compared with predicted rates. As shown in the figure, actual 6-year event rates were similar to 10-year predicted rates for the FRS and were similar to or exceeded predicted rates for the ACC/AHA risk score.



Conclusions: Our findings suggest that CVD risk prediction scores designed for the general population, and particularly the new ACC/AHA risk score, may underestimate risk for HIV-infected patients. Accurate CVD risk prediction is an important component of the long-term management of chronic disease complications in HIV.

863 Specific Effects of ZDV, 3TC and LPV/r on HIV-1 RNA Viral Load During Pregnancy

Patumrat Sripan[1]; Sophie Le Coeur[5]; Lily Ingsrisawang[2]; Tim R. Cressey[3]; Jean-Marc Tréluyer[6]; Naïm Bouazza[4]; Frantz Foissac[4]; Gonzague Jourdain[3]; Marc G. Lallemant[3]; Saïk Urien[7]

[1]ED420, University of Paris Sud 11, Paris Descartes, Paris, France/PHPT-IRD UMI 174, Chiang Mai, Thailand/Department of Statistics, Faculty of Science, Kasetsart University, Bangkok, Thailand; [2]Department of Statistics, Faculty of Science, Kasetsart University, Bangkok, Thailand; [3]PHPT-IRD UMI 174, Faculty of Associated Medical Sciences, Chiang Mai University/Harvard School of Public Health, Chiang Mai, Thailand; [4]EA 08 Université Paris Descartes, Sorbonne Paris Cité, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, Paris, France; [5]Institut d'Etudes Démographiques, Institut de Recherche Pour le Développement (UMR 196 CEPED), Paris, France/Harvard School of Public Health, Boston, MA, USA/Faculty of Associated Medical Science, Chiang Mai University, Chiang Mai, Thailand; [6]EA 08 Université Paris Descartes, Sorbonne Paris Cité, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, Service de Pharmacologie Clinique, AP-HP, Groupe Hospitalier Paris Centre, CIC-0901 Inserm, Cochin-Necker, Paris, France; [7]EA 08 Université Paris Descartes, Sorbonne Paris Cité, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, CIC-0901 Inserm, Cochin-Necker, Paris, France

Background: HIV-infected women commonly receive zidovudine (ZDV) + lamivudine (3TC) + lopinavir/ritonavir (LPV/r) during pregnancy for the prevention of mother-to-child transmission (PMTCT) in Thailand. Our aims were to evaluate the role of 3TC added to ZDV+LPV/r and the specific effect of each drug on maternal HIV-1RNA viral load (VL) reduction for the PMTCT.

Methods: A total of 1,655 plasma VL levels from 702 pregnant women enrolled in the PHPT-5 perinatal HIV prevention trial in Thailand (NCT01511237, NCT00409591) were included. ART naïve pregnant women received either (1) ZDV only (plus nevirapine at onset of labor); (2) ZDV+LPV/r; or (3) ZDV+3TC+LPV/r. HIV-1 RNA VL time courses were analysed using non-linear mixed effect modelling and dependent on VL at treatment initiation and duration of treatments. An Emax response model was used to describe the impact of these ARV regimens on VL reduction during pregnancy. A mechanistically-based equation was developed to determine the contribution of each drug assuming ZDV and 3TC have the same target and mechanism of action, and the effect of LPV/r was added as a separate component.

Results: Of the 702 women, 278 (40%) received ZDV monotherapy, 146 (20%) ZDV+LPV/r and 278 (40%) ZDV+3TC+LPV/r during pregnancy. The maximum effect of each regimen on HIV-1 RNA VL was significantly different ($p<0.02$), with 1.67, 3.8 and 4.57 log_{10}copies/mL reduction for ZDV alone, ZDV+LPV/r and ZDV+3TC+LPV/r, respectively. Time to reach half of maximum effect (T_{50}) was significantly longer with ZDV alone compared with ZDV+3TC+LPV/r ($p<0.001$). However there was no significant difference between ZDV+LPV/r and ZDV+3TC+LPV/r ($p=0.13$). The mechanistically-based model estimated that 110 days of ZDV or 3TC were necessary to achieve half of ZDV or 3TC maximum effect on viral load suppression (maximum effect: minus 1.38 and 2.05 log_{10}copies/mL, respectively) whereas only 10 days of LPV/r were necessary to achieve half of LPV/r maximum effect (maximum effect: minus 2.32 log_{10} copies/mL). Using the mean VL at treatment initiation (4.07 log_{10} copies/mL), the model indicated that the addition of 3TC reduced the time to undetectable VL (<50copies/mL) by 3 weeks: 7.3 weeks with ZDV+LPV/r compared with 4.4 weeks for ZDV+3TC+LPV/r assuming a common T_{50} for ZDV and 3TC.

Conclusions: The addition of 3TC to ZDV+LPV/r during pregnancy reduces time to reach undetectable VL in pregnant women, especially those with a high VL at treatment initiation and subsequent high risk of MTCT.

864 Viral Suppression After Antiretroviral Therapy Initiation in Pregnancy in South Africa

Landon Myer[1]; Tamsin Phillips[1]; Nei-Yuan Hsiao[2]; Allison Zerbe[3]; Jo Ramjith[1]; Linda-Gail Bekker[1]; James A. McIntyre[4]; Elaine J. Abrams[3]

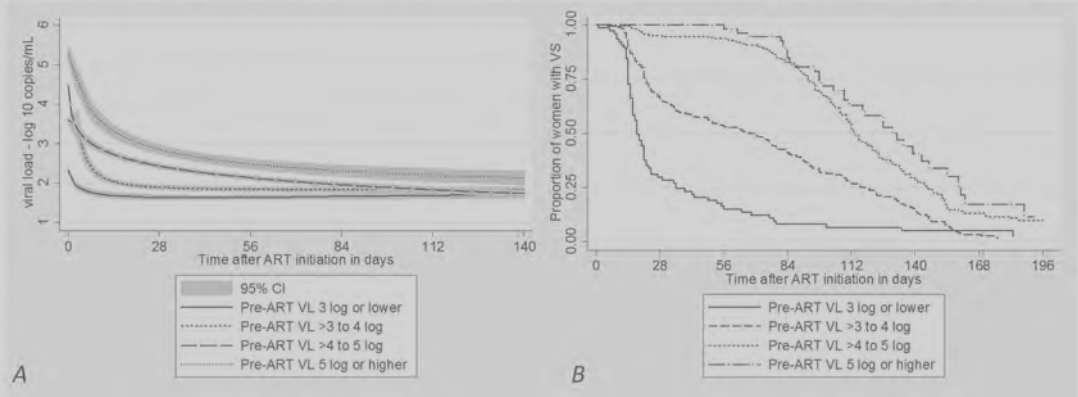
[1]University of Cape Town, Cape Town, South Africa; [2]National Health Laboratory Services/University of Cape Town, Cape Town, South Africa; [3]ICAP at Columbia University, New York, NY, US; [4]Anova Health Institute, Johannesburg, South Africa

Background: HIV viral load (VL) is the principle determinant of mother-to-child transmission (MTCT) risk and rapid lowering of VL is a primary goal of antiretroviral therapy (ART) for prevention of MTCT. However there are few data on the trajectory of viral load (VL) and time to viral suppression <50 copies/mL (VS) following ART initiation in HIV-infected pregnant women.

Methods: Consecutive pregnant women initiating ART in Cape Town, South Africa were recruited into a prospective cohort from ART initiation through delivery, with VL measured immediately prior to initiation (pre-ART), 1-4 weeks after initiation, during the 3rd trimester, and at 1 week postpartum. All women initiated TDF+FTC+EFV. Analyses examined changes in log VL trajectories after initiation using non-linear mixed models, the proportions of women achieving VS over time using product-limit methods, and the probability of VS at delivery using logistic regression.

Results: From April 2013 to May 2014, 629 ART-naïve pregnant women were enrolled (median age, 28 years; median CD4 cell count, 343 cells/μL; median gestation age (GA), 21 weeks; median VL, 4.0 log10 copies/mL [IQR: 3.4-4.6]). Most women achieved VL<3 log within 4 weeks of ART start (Figure 1a) but the median time to VS<50 copies/mL was 14.1 weeks (95% CI, 13.3-15.3). Time to VS was strongly influenced by pre-ART VL: women with VL <3, 3-4, 4-5 and >5 log10 copies/mL before ART initiation had median times to VS of 2.9, 9.6, 17 and 18.9 weeks, respectively ($p<0.001$; Figure 1b). 75% of women achieved VS by delivery. Adjusting for age and past ARV exposure, decreased probability of VS at delivery was associated with higher pre-ART VL (relative odds [RO] 0.39 for a 1-log increase in pre-ART VL, $p<0.001$); later GA at ART initiation (RO, 0.87 for a 1-week increase in GA at ART initiation, $p<0.001$); and inversely associated with higher pre-ART CD4 cell counts (RO, 1.08 for a 50-unit increase in pre-ART CD4 cell count, $p=0.025$).

Figure 1. Viral load declines following ART initiation in pregnancy: (a) fractional polynomial modelling of VL declines over time and (b) time to viral suppression <50 copies/mL, by pre-ART VL categories



Conclusions: These data provide novel evidence on VS after ART initiation in pregnancy in African populations using a standardised first-line regimen. The rapid early declines in VL to <3 log within a month on ART in most women are encouraging. However one-quarter of the cohort still had detectable VL at the time of delivery, demonstrating the importance of early initiation of ART in pregnancy.

865 Maternal Viral Load in the Context of PMTCT B+ Within the Kabeho Study in Kigali

Emily A. Bobrow[1]; Placidie Mugwaneza[2]; Gilles F. Ndayisaba[3]; Dieudonne Ndatimana[3]; **Michelle Gill**[1]; Heather J. Hoffman[4]; Cyprien Baribwira[5]; Laura Guay[1]; Anita Asiimwe[6]
Kabeho Study Team

[1]Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, US; [2]Ministry of Health, Kigali, Rwanda; [3]Elizabeth Glaser Pediatric AIDS Foundation, Kigali, Rwanda; [4]George Washington University Milken Institute School of Public Health, Washington, DC, US; [5]University of Maryland, School of Medicine, Kigali, Rwanda; [6]Rwanda University Teaching Hospitals, Kigali, Rwanda

Background: In April 2012, Rwanda started to implement a policy to initiate HIV-positive pregnant women on lifelong antiretroviral treatment (ART) ('Option B+'). In April 2013, EGPAF and the Ministry of Health began the Kigali Antiretroviral and Breastfeeding Assessment for the Elimination of HIV (Kabeho) Study. The study will determine 18 and 24 month HIV-free survival of a cohort of HIV-exposed children in the PMTCT program.

Methods: From April 2013-January 2014, 608 HIV-positive women on triple drug ART in the third trimester of pregnancy or within two weeks post-delivery were enrolled in the observational prospective cohort from 14 health facilities in Kigali. After providing written informed consent, women underwent enrollment, including HIV and ART-related history and adherence, and a blood draw for viral load (VL) testing by RNA-PCR (Roche).

Results: The median time women knew their HIV-positive status was 38.0 months (IQR 4.7–83.5). The most common ARV regimen (56.6%, 344/608) was TDF/3TC/EFV. Overall, 35.2% (n=214) of women reported taking another regimen previously; 21.5% (n=130) due to PMTCT during an earlier pregnancy. At enrollment, women were on ART for a median of 13.4 months (IQR 2.96–48.8); median time on current ART was 9.2 months (IQR 2.3-34.8). The adherence rate based on a 3-day ART recall was 90.9%. Side effects were reported in the past month by 17.5% (n=105) of women, with dizziness as most common (n=53).

Half of women (52.2%, 316/606) had undetectable VL. Figure 1 shows the distribution of VL by ART duration. Logistic regression using GEE (N=579) indicates women were more likely to have a detectable VL if they had no education (AOR=2.21, 95% CI: 1.31, 3.73), reported side effects in the past month (AOR=1.96, 95% CI: 1.37, 2.81), and had been on ART less than four months, when compared to those with ART exposure from 4-12 months (AOR=3.98, 95% CI: 2.11, 7.50), 12-24 months (AOR=6.04, 95% CI: 2.47, 14.76), and 24-36 months (AOR=5.57, 95% CI: 2.38, 13.05). VL slightly decreased beyond 36 months on ART (AOR=3.56, 95% CI: 1.69, 7.50).

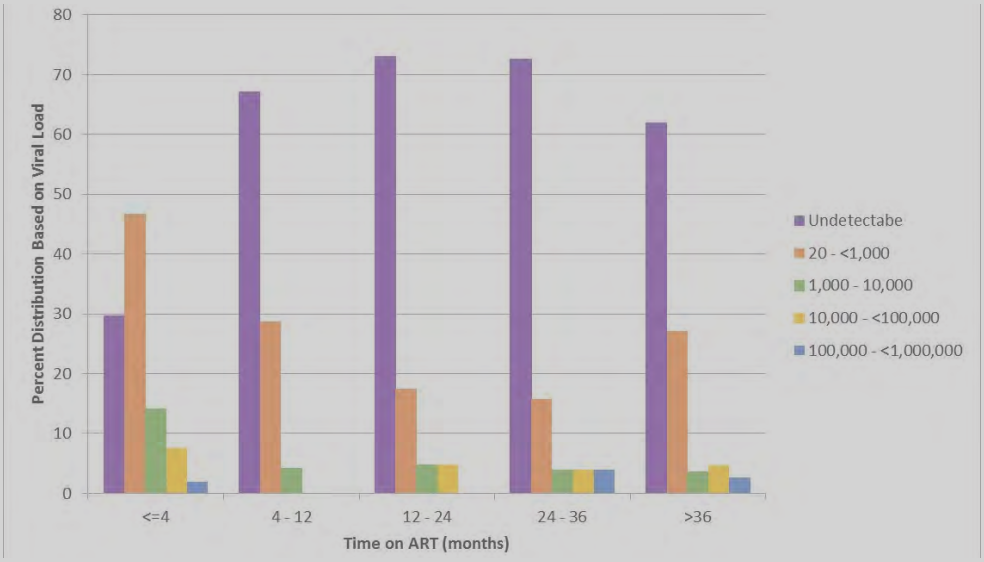


Figure 1. Distribution of viral loads stratified by time on ART.

Conclusions: High rates of ART adherence in the antenatal/peripartum period under Option B+ were reported. However, only half of women had undetectable VL at enrollment. Findings suggest longer ART duration may be needed for women in PMTCT to achieve viral suppression. Testing for ARV resistance is planned. Analysis of the cohort will incorporate specific regimen information, regimen changes, longitudinal VL, and adherence over time.

866 ART Response Among Pregnant and Postpartum Women With Acute Versus Chronic HIV-1

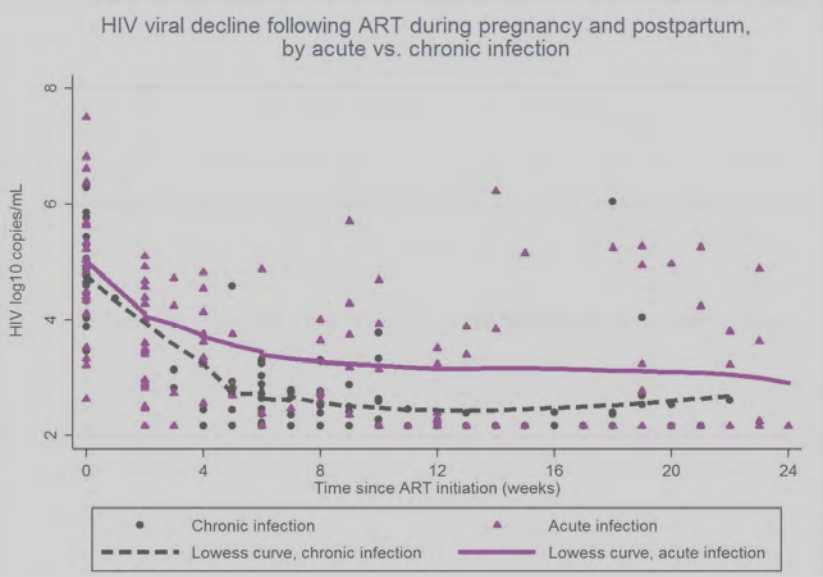
Alison L. Drake[1]; John Kinuthia[2]; Daniel Matemo[2]; Barbra Richardson[1]; Michael Chung[1]; James N. Kiarie[2]; Sandy Emery[3]; Julie M. Overbaugh[3]; Grace John-Stewart[1]

[1]University of Washington, Seattle, WA, US; [2]University of Nairobi, Nairobi, Kenya; [3]Fred Hutchinson Cancer Research Center, Seattle, WA, US

Background: Risk of mother-to-child HIV-1 transmission (MTCT) is high among women with acute HIV-1 infection (AHI). Plasma HIV-1 viral load (PVL) can be substantially reduced with antiretroviral therapy (ART), which reduces MTCT risk; however, viral decline post-ART among pregnant and postpartum women with AHI has not been well characterized. We compared virologic and immunologic responses to ART between pregnant and postpartum women with AHI versus chronic HIV-1 infection (CHI) in Kenya.

Methods: Women with AHI (detected by nucleic acid amplification tests conducted serially during pregnancy and postpartum) initiating ART (3TC, EFV, and either ZDV or TDF) were identified in a prospective study in Western Kenya. Women with CHI who initiated ART (AZT, 3TC, and NVP) during pregnancy in a prior clinical trial in Nairobi and had available PVL and CD4 data were selected for comparison. Blood was collected serially in both studies to compare post-ART changes in PVL and CD4; PVL was evaluated using the same laboratory and assay for both studies. Linear mixed effects models were used to model rate of PVL decline and demographics and CD4 were compared by the Wilcoxon Rank-Sum Test.

Results: Data from 25 women with AHI and 30 women with CHI were compared. Women with AHI were younger (median 21 vs. 30 years; p=.006) and less likely to be married (97% vs. 76%; p=.02) than women with CHI. Mean baseline PVL was similar (AHI: 4.52, CHI: 4.37 $\log_{10}$copies/mL; p=.5). Baseline CD4 count was significantly higher in women with AHI than CHI (median 542 vs. 267, respectively; p<.001). Average monthly decline in PVL during 10 weeks post-ART was greater among women with CHI (-1.04 $\log_{10}$ copies/mL; 95% Confidence Interval [CI]:-1.50,-0.57) than AHI (-.67 $\log_{10}$copies/mL, 95% CI:-0.84, -0.47); CHI versus AHI PVL decline p=.007), adjusting for baseline CD4. Viral decline was less pronounced 10 to 24 weeks post-ART in both groups, but remained steeper among women with CHI versus AHI (-.15 versus -.03 $\log_{10}$copies/mL, respectively; p=.002). Change in CD4 counts 6 months post-ART was similar (p=.5).



Conclusions: Rate of viral decline following ART was significantly slower among women with AHI than CHI, perhaps because HIV-specific immune responses that work synergistically with ART to decrease PVL have not yet developed in AHI. Strategies to accelerate viral decline, such as ART-intensification among AHI during pregnancy and postpartum, may be useful to reduce MTCT risk.

959 Tenofovir/Emtricitabine Plus LPV/r vs MVC or Raltegravir for PEP: 2 Randomized Trials

Lorna Leal; Agathe Leon; Berta Torres; Alexy Inciarte; Constanza Lucero; Josep Mallolas; Maria Martinez-Rebollar; Ana González-Cordón; Jose M. Gatell; Felipe Garcia

Hospital Clínic Barcelona, Barcelona, Spain

Background: PEP is recommended after a potential exposure to HIV. In animal models, PEP has to be maintained 4 weeks to be effective. However, with the recommended regimens in humans, side effects are frequent and are the main reason for poor adherence and a high rate of discontinuation. The objective of these 2 trials was to assess the rate of discontinuation of PEP at 28 days comparing the standard of care Lopinavir/r (LPV/r) vs Maraviroc (MVC) or Raltegravir (RAL) both with Tenofovir/Emtricitabine (TVD).

Methods: Individuals coming to the emergency room (ER) for potential sexual exposure to HIV were randomized to: TVD 200/245 QD plus LPV/r 400/100 BID (n=117) or plus MVC 300 BID (n=120) in one trial (n=237) and TVD plus LPV/r (n=121) or plus RAL 400 BID (n=122) in the second trial (n=243). After randomization, 4 follow-up visits were scheduled: day 0, 28, 90 and 180. The primary end-point was rate of discontinuation at day 28. Secondary end-points were adherence to PEP, side effects and rate of seroconversions.

Results: In MVC and RAL trials, median age was 35 and 33 years and 92% and 90% were males respectively. The median interval between exposure and presentation at ER was 15h and 13.5h. Type of exposition was male homosexual sex in 83% and 81%. The level of risk was high in only 13% and 9% of individuals. The source patient was known to be HIV infected in 30.8% and 31%. In MVC trial, only 187/237 (79%) who were randomized and started PEP attended the first scheduled visit (day 0) and differences between arms were not observed (p=0.92). Similar results were found in RAL trial [198/243 (81.5%) attended the day 0 (p=0.62)]. The rate of discontinuation of PEP before day 28 of follow-up was significantly higher in LPV/r (31.5%) vs MVC (11.6%) arm (p=0.001) and in LPV/r (36.6%) vs RAL (23.7%) arm (p=0.04). The proportion of patients with low adherence to PEP was similar in LPV/r vs MVC arms (54% vs 46%, respectively, p=0.56), but was higher in LPV/r vs RAL arms (49.2% vs 30.8%, respectively, p=0.03). Adverse effects were reported in 122 out of 187 (50.8%) patients in MVC study attending at least the day 0 visit [70/92 (76.1%) in LPV/r and 52/95 (54.7%) in MVC arm, p=0.002] and in in 134 out of 198 (67.7%) patients in RAL study [75/101 (74.3%) in LPV/r and 59/97 (60.8%) in RAL arm, p=0.04]. No seroconversions were observed.

Conclusions: The rate of discontinuation of PEP and side effects were higher in patients allocated to TVD plus LPV/r as compared with those with TVD plus MVC or TVD plus RAL.

958 Rilpivirine-Emtricitabine-Tenofovir for HIV Nonoccupational Postexposure Prophylaxis

Rosalind Foster[1]; John McAllister[2]; Tim R. Read[3]; Anna Pierce[4]; Robyn Richardson[2]; Anna McNulty[1]; Andrew Carr[2]
On behalf of the EPEP Study Researchers

[1]*Sydney Sexual Health Centre, Sydney, Australia;* [2]*St Vincent's Centre for Applied Medical Research, Sydney, Australia;* [3]*Melbourne Sexual Health Centre, Melbourne, Australia;* [4]*The Alfred Hospital, Melbourne, Australia*

Background: CDC recommends 3-drug post-exposure prophylaxis (PEP) with emtricitabine-tenofovir disoproxil fumarate (FTC-TDF) plus raltegravir (RAL) for 28 days. But in one non-occupational (N)PEP study, FTC-TDF-RAL adherence was imperfect (only 52% took all 3 pills/day) and RAL was associated with acute muscle adverse effects (9%). FTC-TDF coformulated with rilpivirine (RPV) as a single-tablet regimen (STR) is a well-tolerated, once-daily NPEP candidate. A plasma tenofovir (TFV) level >40ng/mL is thought to reflect recent full adherence, whereas a level <10ng/mL suggests no dose for ≥7 days. NPEP studies to date have neither evaluated STRs nor measured TFV levels. We hypothesized FTC/RPV/TDF as an STR NPEP would be safe, well-tolerated, and result in high adherence.

Methods: We evaluated NPEP with STR FTC/RPV/TDF for 28 days in gay men after high-risk, sexual exposure, in an open-label, single-arm study. We assessed adherence (pill count; patient report; and plasma TFV levels at Week 4 in a subset by HPLC), adverse events (AEs) and HIV status through Week 12. Final intention-to-treat (ITT) analyses are reported.

Results: 100 men (mean age 31 years [SD 9]) presented a mean 30 hours (SD 21) after anal sex (88% receptive). NPEP commenced 2 hours (SD 2.3) post-presentation. No participant was HIV+ at enrolment or through Week 12, or ceased NPEP because their 'source' was found to be HIV-negative. NPEP completion was 92% (95%CI 85 to 96); failures occurred at median 14 days for loss to follow-up (6%), adverse event (1%) or study burden (1%). NPEP adherence was 98.6% (SD 2.7) by self-report. In the 78 participants with pill-count data, adherence was 98.7% (SD 2.4). 86% reported taking all doses with food. Of 78 paired assessments available for percent adherence by pill count and self-report, agreement was 100% (kappa=1.0; P<0.0001). From the final 50 participants, plasma TFV was measured within 48 hours of the last dose in 41 (88%) participants who reached Day 28 (mean 16 hrs [SD 10]): 36 (88%) participants had levels >40ng/mL and only 1 (2%) was <10ng/mL. One participant developed pancreatitis 1 day post-NPEP. 5 other participants

developed a Grade 3 AE; 2 possibly due to study drug**.** Grade 3+ lab AEs possibly due to study drug occurred in 2 participants. Mean serum creatinine rose from 83 to 88 μM/L at Day 28 (P<0.001), but with no grade 1+ increase and no significant change in serum phosphate.

Conclusions: STR FTC/RPV/TDF was well-tolerated as once-daily NPEP, with high levels of adherence and completion.

957 Significant Intolerability of Efavirenz in HIV Occupational Postexposure Prophylaxis

Surasak Wiboonchutikul[1]; Varaporn Thientong[1]; Patama Sutha[1]; Boonchai Kowadisaiburana[2]; Weerawat Manosuthi[1]

[1]Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand; [2]Bangkok Hospital, Bangkok, Thailand

Background: Postexposure prophylaxis (PEP) has been used to decrease a risk of HIV transmission after occupational exposure. Regimen completion is one of the most important factors in successful prophylaxis. Limited data are available on tolerability of PEP regimens in healthcare workers (HCWs) in resource-limited settings. We aimed to describe the characteristics of occupational exposure, and sought to determine factors associated with incompletion of the 4-week HIV prophylactic course.

Methods: A retrospective study was conducted among HCWs who accidentally exposed to blood or body fluid of patients at Bamrasnaradura Infectious Diseases Institute, Thailand, between March 1996 and June 2014. The characteristics of exposure were described, and logistic regression analysis was used to determine factors associated with incompletion of the 4-week prophylactic course.

Results: A total of 225 exposure episodes were reported (163 percutaneous injury, 43 mucosal exposure, 6 non-intact skin exposure, and 13 intact skin exposure). The mean (SD) age was 33.1 (9.9) years and 189 (84%) were females. The most frequently exposed groups were nurses (43%), patient or nurse assistants (18%), and medical technicians (15%). The HIV status of the source was defined in 149 (66%) episodes which were positive in 101 (68%). Of 225 exposures, PEP was prescribed in 155 (69%) episodes but was subsequently intentionally discontinued in 26 episodes (HIV source was negative in 19, refusal to continue in 7). PEP courses should have completed in 129 episodes. Of 129 prescribed regimens, 38% were 2 NRTIs, 37% were 2 NRTIs + PIs, 12% were Zidovudine alone, 9% were 2 NRTIs + Efavirenz (EFV), and 4% were 2 NRTIs + Raltegravir. Only 91 of 129 (71%) HCWs were able to complete the 4-week regimen. Multivariate analysis showed that 2 NRTIs + EFV was the only significant factor associated with incompletion of the 4 week-course (OR 33.3; 95% CI 4.2-100; $p < 0.01$). Other factors including age, gender, staff position, status of the source, and other PEP regimens were not associated with incompletion of the 4-week course ($p > 0.05$). The reason for premature discontinuation of 2 NRTIs + EFV was intolerability in all HCWs. None of the HCWs was reported to have HIV seroconversion.

Conclusions: Two NRTIs + EFV regimen was significantly associated with premature discontinuation of occupational PEP. This regimen should not be further used for HIV prophylaxis following occupational exposure in the resource-limited settings.

961 Management of Acute HIV After Initiation of Postexposure Prophylaxis: Challenges and Lessons Learned

Goli Haidari[1]; Naomi Fitzgerald[4]; Sonia Raffe[2]; Nneka Nwokolo[3]; Olamide Dosekun[1]; Mark D. Lawton[5]; Nickie Mackie[1]; Julie Fox[4]; Martin Fisher[2]; Sarah Fidler[1]

[1]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom; [2]Brighton and Sussex Hospitals NHS Trust, Brighton, United Kingdom; [3]Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom; [4]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [5]The Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, United Kingdom; [6]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom; [7]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [8]Brighton and Sussex Hospitals NHS Trust, Brighton, United Kingdom; [9]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom

Background: International guidelines recommend HIV post exposure prophylaxis following sexual exposure (PEPSE) to prevent HIV infection. However, methods to screen for infection prior to initiating PEPSE are less clear, with little or no guidance for management of acute HIV diagnosed during PEPSE. We present a case series of individuals diagnosed HIV+ whilst on PEPSE.

Methods: Cases definitions include the following criteria:

1. PEPSE failure: negative point of care test (POCT) and 4th generation laboratory test at PEP start, with HIV diagnosed during PEP or in follow up period

2. Acute HIV infection at PEPSE initiation: negative POCT but subsequent reactive 4th generation test at PEP start

Results: 18 patients identified; 17 male/1 female, mean age 34 years. 11/18 (67%) had a previous negative HIV test using laboratory Abbott Ab/Ag tests, 1/18 POCT, in the preceding 12 months to accessing PEP. 18/18 were prescribed NRTI + bPI, 16 of these in line with current UK guidelines.

From data available on 16 (2 not diagnosed at our trusts), HIV diagnoses were subsequently made using laboratory Ab/Ag test in 14/16, POCT in 1 and HIV RNA in 1. 1/18 tested negative by POCT and Ab/Ag lab tests at PEP start, subsequently tested HIV+ with a weakly reactive p24 antigen and positive HIV-RNA on laboratory testing 19 days after completing a 28 day PEP course. The remaining 17 patients initiated PEP based on a negative POCT or recent negative HIV antibody test but were subsequently diagnosed HIV+ using lab tests . Therefore 17/18 (94%) of patients were already HIV+ at PEP initiation.

Of those diagnosed HIV+ whilst still on PEP, 11/16 (68%) opted to continue ART. A decision was made to stop PEP in 5 patients (mean number of days on PEP; 10); this advice was not influenced by CD4 or HIV RNA. 5/11 switched PEP regimes to first line ART. 2/18 had drug resistance: K103N, T215D at diagnosis.

Conclusions: Patients presenting for PEP after sexual exposure are high-risk individuals who may be seroconverting at the time of presentation. It is essential that if a POCT is used at screening, this is accompanied by a 4th generation test as near to initiation as possible, and that dual therapy (as still recommended in some guidelines) must be avoided in this setting.

Acute HIV diagnosis whilst on PEP represents an opportunity for early ART with reduction of viral reservoirs and improvements in CD4 outcome. In the absence of specific data to inform best practice, we recommend continued ART until urgent review by an HIV specialist.

Session S-7 Symposium Room 613

4:00 pm – 6:00 pm

From Pathways to Paradigms: Applications of Systems Biology to HIV/Host Interactions

171 Using Systems Approaches to Study Pathogenesis: Bridging Networks and Mechanisms

Nevan Krogan

University of California San Francisco, San Francisco, CA, US

There is a wide gap between the generation of large-scale biological data sets and more-detailed structural and mechanistic studies. However, recent work that explicitly combine data from systems and structural biological approaches is having a profound effect on our ability to predict how mutations and small molecules affect atomic-level mechanisms, disrupt systems-level networks and ultimately lead to changes in organismal fitness. Our group aims to create a stronger bridge between these areas primarily using three types of data: genetic interactions, protein-protein interactions and post-translational modifications. Protein structural information helps to prioritize and functionally understand these large-scale datasets; conversely global, unbiasedly collected datasets helps inform the more mechanistic studies. Recently, we have been studying the host-pathogen interface

using a series of proteomic and genomic approaches, which has revealed insight into global mechanisms of pathogenesis but has also uncovered important specific insight into the how specific pathogenic proteins re-wire the host during infection. Effort is now ongoing to connect this information to clinical data especially to sequence information from relevant cohorts. Recent progress in these areas will be discussed.

172 Molecular Basis of T-Cell Exhaustion

E. John Wherry

University of Pennsylvania, Philadelphia, PA, US

T cell exhaustion is common during chronic infections in animal models and in humans as well as in cancer and can prevent optimal immunity. Exhausted T cells are defined by the loss of ability to perform effector functions efficiently, low proliferative capacity and poor survival following antigen stimulation. In addition, it has become clear that exhausted T cells co-express multiple inhibitory receptors that negatively regulate their function. Indeed, receptors such as PD-1 have become major targets of clinical immunotherapies in cancer and infectious disease aimed at re-invigorating exhausted T cells. We have used genomic and systems biology approaches to define transcriptional networks of T cell exhaustion revealing key molecular pathways, modules and central "hub" genes involved in this state of T cell dysfunction. Recent work has focused on the role of centrally involved transcription factors, including T-bet and Eomesodermin (Eomes). T-bet and Eomes control a proliferative hierarchy necessary to maintain exhausted T cell populations during chronic infection where these subsets of exhausted T cells exert partial ability to contain, but not control chronic viral replication. Moreover, our studies revealed unique context-specific functions for T-bet and Eomes since these transcription factors are associated with different roles in functional memory T cells. Additional studies are focusing on the role of other transcription factors as well as the molecular and systems biology signatures of reversal of T cell exhaustion. Ultimately, a more precise molecular understanding of T cell exhaustion should lead to novel and more robust clinical interventions to reverse or prevent exhaustion in settings of persisting infections such as HIV.

173 A Systems Biology Approach to Identify Targets and Mechanisms of HIV Latency and HIV Eradication

Rafick P. Sekaly

Case Western Reserve University, Cleveland, OH, US

There is intense interest in developing safe and scalable curative interventions for Berlin patient has paved the way to identify therapeutic interventions that can lead to eradication of HIV. This goal can only be achieved by identifying the cellular localization of the HIV reservoir, the molecular mechanisms that result in the establishment and maintenance of latent infection and host determinants that dictate who might or might not respond to curative interventions. We have used an unbiased system biology approach to identify signal transduction pathways and transcriptional nodes that can predict the size of the HIV reservoir—as estimated by integrated HIV DNA levels—in a large cohort of long-term antiretroviral-treated adults. We show that distinct intracellular pathways associated with cell metabolism, activation and differentiation predict the estimated size of the reservoir. We found that upregulation of TGF-beta was associated with higher reservoir size, and validated the importance of the TGF-beta pathway in vitro using a primary T cell model of HIV latency. Finally we have shown that a specific subgroup of subjects who fail to reconstitute their immune system after ART (immune non-responders) have significantly higher levels of HIV replication competent latent HIV . We show using integrated OMICs approaches that the balance between FOXO3A and IRF-7 is a correlate of immune reconstitution and the size of the reservoir. System biology approaches have proven an essential tool in providing highly relevant clues that could lead to the identification of novel curative interventions. This work was funded by grants from the NIH U19 AI096109, Merck Research Laboratories, and the Fasenmayer Foundation.

Khader Ghneim, Jessica Brehm,Aarthi Talla, Slim Fourati, Deanna Kulpa Nicolas Chomont,Daria Hazuda, Steve Deeks and Michael Lederman. Case Western Research University, Merck Research Laboratories, Universite de Montreal, VGTI Florida and University of California, San Francisco

174 Translating Anti–HIV-1 Immune Mechanisms Into Clinical Interventions

Sallie R. Permar

Duke University, Durham, NC, US

HIV-1 transmission occurs in a complex *in vivo* setting, with innate and adaptive immunity, host genetics, and virus diversity all contributing to the risk of virus acquisition. As we expand our repertoire of techniques to measure HIV-1-specific immune responses and viral and host factors, we have both sharpened our ability to dissect the protective role of HIV-1-specific immune responses, as well as clouded the picture through measurement of immune responses and host factors with overlapping functions and roles. Thus, novel methods are needed to probe immune mechanisms that underlie the measured immune responses with overlapping, redundant, and correlated functions to make predictions about the unmeasured immune phenomenon that may contribute to interrupting HIV-1 transmission *in vivo*. Maternal antibody is known to protect the infant against acquisition of microbial pathogens, yet the role of maternal antibody in protection against mother to child transmission of HIV-1 remains unclear. In this talk, I will discuss our application of multivariable immune correlate analysis to cohorts of HIV-1-transmitting and non-transmitting women and the insights gained on the role of both the measured immune responses that associated with reduced transmission risk and the underlying immune mechanisms on vertical HIV-1 transmission. Moreover, I will discuss strategies to further probe the hypotheses generated by these immune correlate analyses in both nonhuman primate and human studies. Insights gained from detailed analysis of immune correlates and studies of their underlying mechanisms combined with strategies for hypothesis testing can inform the next generation of immune-based interventions to prevent or treat HIV-1 infection.

Session S-8 Symposium — Room 6D

4:00 pm – 6:00 pm

Scale-Up of Interventions

175 From Equipoise to Efficacy to Millions Reached With Voluntary Medical Male Circumcision for HIV Prevention

Jason B. Reed

US Department of State, Office of the Global AIDS Coordinator, Washington, DC, US

Data from three randomized controlled trials in sub-Saharan Africa demonstrated voluntary medical male circumcision (VMMC) reduces males' risk of HIV acquisition by approximately 60%, making it one of the most effective HIV prevention interventions. VMMC also reduces the risk of several sexually transmitted infections (STI) in males and their female partners, and reduces females' HIV risk as their probabilities of encountering HIV-infected male sexual partners decrease.

In 2011, WHO and UNAIDS set a target of reaching 80% circumcision coverage among males aged 15-49 years in 14 priority countries in east and southern Africa, equivalent to over 20 million VMMCs by the end of 2016. According to mathematical models, this could avert 3.4 million new HIV infections within 15 years and save up to US$16.5 billion in HIV care and treatment costs. Through the end of U.S. fiscal year 2014, PEPFAR had supported more than 6.5 million VMMCs in the priority countries.

Strategic priorities within VMMC scale up have evolved as programs matured. Stakeholders have progressively focused on: community engagement and sensitization; establishing favorable policy environments; instituting safe surgical services and safety monitoring systems; and, balancing supply and demand in continually expanding programs. As experience has grown, global and national stakeholders expanded focus to identify supply- and demand-side efficiencies through implementation research and delivery science.

Population-based survey and study data show disproportionately low health service uptake among men, including poor HIV-related service uptake and outcomes. VMMC is uniquely positioned to initiate positive health system encounters and support HIV case finding among males who may not otherwise test for HIV. As care and treatment programs endeavor to achieve the UNAIDS 90-90-90 goals by 2020, it will be important to maximally leverage the VMMC platform to help ensure requisite male representation within the treatment cascade.

Global health resources, including those for VMMC, are under increasing scrutiny to deliver demonstrable impact. Continued investment in VMMC will require refocusing efforts on intensifying HIV incidence reductions by prioritizing geographic areas and age groups according to HIV risk. Offering VMMC to those most at risk achieves epidemic control with fewer procedures and keeps VMMC on pace to support the UNAIDS goal of ending the global AIDS epidemic by 2030.

176 Scale-Up of HIV Interventions for People Who Inject Drugs: Quality and Coverage

Anna Deryabina

ICAP at Columbia University, Almaty, Kazakhstan

It is estimated that, of the estimated 13 million people who inject drugs (PWID) worldwide, 13% are living with HIV. Eastern Europe, Central Asia, South and South East Asia have the largest injection drug-use driven HIV epidemics. However, recent data show an increasing role of injection and non-injection drug use in HIV transmission in several African countries, including South Africa, Kenya and Tanzania. Criminalization of drug use, restrictive drug policies, aggressive law enforcement practices and lack of availability of harm reduction as well as HIV prevention, care and treatment programs for PWID undermine the ability to respond effectively to the HIV epidemic among PWID. The recommended package for PWID includes nine interventions, four of which (needles and syringe programs, opioid substitution therapy (OST) programs, HIV testing and counseling, and antiretroviral therapy (ART)) are core and have synergistic impact of reducing HIV transmission and enhancing outcomes among PWID with HIV. However, in many countries availability and access to evidence-based interventions remains limited. In many of the most affected countries programs like OST remain small-scale pilots, while coverage of eligible PWID with HIV prevention interventions and ART remains by far insufficient to effectively control the epidemic in this population. Rapid scale-up of effective interventions to reduce drug consumption and unsafe injecting practices is needed to prevent further spread of HIV among PWID, their intimate partners and the society in general. Scale up is about quality and comprehensiveness of services delivered. Effective and comprehensive programs to prevent HIV transmission from PWID to others include implementation of accessible HIV testing and counseling services, including rapid HIV testing, prompt initiation of ART, especially among those living in discordant couples, and scale up of OST programs to reduce HIV burden among PWID; and for PWID living with HIV to enhance their engagement and adherence to HIV treatment. Scale up is also about access and engaging PWID in the design and implementation of programs and prioritizing health of individuals and health of the community at all level of decision-making and implementation. Programs need to ensure that HIV interventions are low-thresh hold, utilize innovative and flexible models to meet the needs of PWID.

177 HIV Testing and Counseling: Emerging Issues, New Directions

Rachel C. Baggaley

World Health Organization, Geneva, Switzerland

With 14 million people on ART the push is now to reach the remaining estimated 20 million who are living with HIV, many of whom are undiagnosed. The UNAIDS 90-90-90 target aims for 90% of all people living with HIV to know their status by 2020. 33% more people were tested in 2013 compared with 2009, however it is estimated that over half (54%) of people with HIV are still unaware of their status.

Routine offer of provider initiated testing and counselling (PITC), recommended by WHO since 2007, is widely accepted in ANC and TB services, including in countries with low HIV prevalence, but has not been as well adopted in other clinical settings, even where HIV prevalence is high. This has led to disparities in testing: men, adolescents and people from key populations are less likely to be reached by HTC through clinical services, resulting in lower testing coverage and later access to HIV care. Reliance on testing through clinical services also partly explains the persistent late presentation of people living with HIV to care.

In 2013 WHO recommended that countries expand testing to include a range of community based approaches to overcome PITC limitations. Approaches to reduce structural and legal barriers to community HTC include legitimising lay testing and the use of rapid tests outside clinical settings; exploring effective HIV self-testing models; and reviewing age of consent to support adolescent testing. Recent approaches to increase the proportion of people diagnosed include community-based testing accompanied by geographic prioritization and targeting populations at greatest risk and partner and family testing. Recent evidence also points to several interventions to rationalize and simplify re-testing for those at ongoing risk and better link people to HIV prevention and care.

In response to emerging evidence of significant problems with testing quality, with reports of up to 7% false positive diagnoses of HIV in people being offered ART, WHO re-emphasised its recommendation to all countries to re-test all people before initiating ART. The causes of these misclassifications and measures to reduce them are being explored to avoid the social and public health consequences of misdiagnosis. HTC approaches have evolved and a range of complementary strategies are now available to reach greater numbers of people. HTC is the first step in both accessing care and preventing further transmission. It will be key to achieving global targets.

178 Ten Years of Strengthening Laboratory Services and Systems: Then, Now, and the Future

John Nkengasong

US Centers for Disease Control and Prevention, Atlanta, GA, US

The last 10 years have been transformational for laboratory medicine in Africa thanks to increase in global health funding, especially from the world bank, PEPFAR, the Global fund—etc. Laboratory networks have been established, systems developed, and human competent work force developed —etc. In fact a recent Institute of Medicine (IOM) report has described laboratory health system strengthening as a "signature achievement" for PEPFAR and also concluded that the progress in strengthening laboratory medicine has also impacted other health systems.

The talk will expand on some of these aspects and address key challenges that remain. It will also demonstrate how laboratory systems build for HIV are being leveraged on to support other program areas such as global health security and TB.

Session S-9 Symposium
Room 6E
4:00 pm – 6:00 pm

HCV: New Frontiers and Controversies

179 Pathogenesis of Acute HCV Infection

Ashwin Balagopal

Johns Hopkins University School of Medicine, Baltimore, MD, US

Hepatitis C virus (HCV) infects 170 million people worldwide; most persons who are acutely infected will develop chronic infection, while 25% of people will spontaneously clear the virus. Because of common routes of transmission, HIV-1/HCV co-infection is highly prevalent. In HIV-1/HCV co-infection, the likelihood of spontaneous clearance is worsened. While we do not fully understand the mechanisms underlying spontaneous clearance versus viral persistence, recent progress has uncovered a number of contributing factors: persons at highest risk for developing chronic HCV infection are older, male, and of African descent. The racial predisposition is partly explained by recently discovered genetic markers in the Interferon Lambda (*IFNL*) gene locus, which are among the most strongly predictive genetic markers of susceptibility to an infectious disease. There has been some progress in identifying the cause underlying the *IFNL* cluster of genes, although questions still remain. Notable defects have also been found in cytotoxic T cells and NK cells that may contribute to HCV persistence. When studying hepatitis C under the microscope, we have seen evidence of clustered infection of hepatocytes, strongly suggesting that local processes foster hepatitis C propagation.

Several clinical controversies have emerged in the management of acute HCV infection. Although public health measures have been effective at attenuating the incidence of acute HCV transmission in urban centers, there is evidence that increased rates of injection drug use in non-urban and rural settings has resulted in emerging outbreaks in these settings. There has also been evidence of outbreaks of acute HCV among HIV-1 infected men who have sex with men. With respect to treatment in the era of direct-acting antivirals, there has been discussion about whether universal treatment should be recommended: currently, AASLD/IDSA guidelines continue to support a period of monitoring patients for spontaneous clearance. However, as therapies evolve, it is likely that more patients will be treated during the acute period.

180 HCV Treatment as Prevention: Challenges and Opportunities

Gregory Dore

University of New South Wales, Sydney, Australia

Major recent advances in hepatitis C virus (HCV) therapeutic development, with highly curative well tolerated all oral regimens now available have raised the prospect that treatment could provide considerable prevention impact. Mathematical modelling has demonstrated that rapid scale-up of interferon-free direct acting antiviral (DAA) therapy among people who inject drugs (PWID) to levels of 4-8% treated per annum would lead to near elimination of HCV within 20 in settings with a chronic HCV prevalence of 25-50%.

Concerted efforts in several areas are required to enhance the feasibility of HCV treatment as prevention. HCV therapeutic regimens with pangenotypic activity, single daily dosing and short duration (4-6 weeks) would be optimum. HCV screening rates need to be increased, particularly among PWID and HIV-infected men who have sex with men (MSM). HCV treatment infrastructure needs to be broadened to provide access through community-based clinics, drug and alcohol services, harm reduction facilities, and prisons. Community engagement including peer-based worker involvement in HCV screening, disease assessment and treatment delivery programs needs to be developed. Finally, drug price reform and public health advocacy will be instrumental to enable levels of HCV treatment coverage among marginalised populations that would provide major prevention impacts.

Two major Australian HCV treatment as prevention initiatives will be described. The SToP-C project is evaluating HCV treatment as prevention in the prison system in New South Wales. A surveillance phase will monitor HCV incidence in four prisons (two maximum security, two medium security), followed by rapid scale-up of interferon-free DAA therapy with ongoing monitoring of HCV transmission. The CEASE project is evaluating HCV treatment as prevention within the HIV-infected population, predominantly MSM. Components include characterisation of the HIV/HCV population through an observational database (CEASE-d), surveillance for newly acquired HCV and modelling (CEASE-m), education of HIV prescribers in HCV management (CEASE-e) and scale-up of HCV treatment (CEASE-t).

181 HCV Therapeutics: It's the Virus, Stupid

Mark Sulkowski

Johns Hopkins University School of Medicine, Baltimore, MD, US

In 1986, Hoofnagle and coworkers reported the initial use of recombinant interferon alfa to treat patients with non-A, non-B hepatitis, demonstrating improvement in serum ALT levels in most patients. Over the ensuing decade, hepatitis C virus was identified cause of non-A, non-B hepatitis and molecular techniques were applied to test HCV RNA response during therapy, and it became apparent that the majority of persons treated with interferon alfa did not achieve HCV eradication (Sustained Virologic Response, SVR). Further, the poor safety and tolerability of interferon alfa prohibited treatment of many HCV-infected patients. In 1995, several studies demonstrated that the addition of the guanosine nucleoside analogue ribavirin to interferon led to higher SVR rates despite the lack of HCV RNA reduction with ribavirin monotherapy. In 2003, the first report of a potent direct acting antiviral (DAA), an inhibitor of the HCV NS3/4A protease known as BILN 2061, was published, and, in 2011, two HCV NS3/4A protease inhibitors, telaprevir and boceprevir, entered clinical practice as part of "triple therapy" with interferon/ribavirin, and, while toxicity limited their effectiveness, the DAA era was launched. In 2012, proof of HCV eradication by the interferon-free, combination of a HCV NS3/4A protease inhibitor and a NS5A inhibitor was published. In 2015, multiple, interferon-free, combinations of DAAs targeting HCV nonstructural proteins (e.g.,NS3/4A protease, NS5B polymerase and NS5A) have been approved by regulatory authorities. Remarkably, 12 weeks of treatment with these DAA regimens can deliver high rates of HCV cure (> 95%) with minimal adverse effects in diverse range of patients including those with HIV coinfection and decompensated liver disease. In this era, historical barriers to HCV cure linked to the necessity for interferon alfa have been overcome. In their place, new challenges have emerged including the cure of persons with HCV genotype 3 infection and those with advanced liver disease among whom SVR rates are lower than observed in other patient groups as well as the specter of HCV drug resistance in persons who fail to achieve HCV eradication following treatment. However, the greatest challenge will be the need to rapidly translate these remarkable advances in HCV therapeutics to the large global community of persons chronically infected with hepatitis C to prevent the development of life-threatening complications of HCV disease.

182 HCV Therapeutics: Big Sticks With Big Stickers

Marion G. Peters

University of California San Francisco, San Francisco, CA, US

The new all oral direct acting antiviral agents (DAA) for HCV have permanently changed the treatment landscape for patients with Hepatitis C (HCV). Because of better tolerability, fewer side effects and shorter length of therapy, the majority of HCV patients are now eligible for treatment and most patients who know they have HCV are eager to be treated.

However these drugs are expensive. Health care systems throughout the world are trying to determine how and to whom to provide HCV therapy. While those with severe disease clearly are in greatest need, recent data has revealed benefits in morbidity and mortality even in those without severe fibrosis. In addition, extrahepatic benefits accrue with

successful eradication of HCV. Cost effectiveness studies have shown DAA to be cost effective. The cost and range of prices of DAAs vary dramatically in, and within, the USA, and throughout the world. There is great diversity in how individual countries have tackled the problem of cost and access for their HCV patients.

Additionally, access to drug in resource-limited countries may be affected by access to diagnostics and care. Some countries and providers have included HCV care in already existing HIV settings while others do not know the extent of their HCV epidemic. Cost studies must include the cost of diagnostics and clinical care as well as the cost of DAAs. Generics and pan genotypic DAAs may well reshape access in resource limited countries. As more DAAs enter the market, cost adjustments may be made which will increase access to HCV treatment.

The impact of SVR on all cause mortality appears to show a clinical and cost effective benefit in treating early, beyond the benefit of stopping fibrosis progression and preventing further liver disease manifestations. These benefits will influence who to treat and cost benefit effectiveness analyses in the future.

POSTER ABSTRACTS

TUESDAY, FEBRUARY 24, 2015

Session P-A1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Cellular Innate Immunity

183 STAT5 Inhibition Reduces HIV-1 Infection and TLR7/8 Responses in Human Macrophages

Sofia Appelberg[1]; Carla N. Mavian[1]; Julie C. Williams[1]; Philip Lichlyter[1]; John Sleasman[2]; Maureen M. Goodenow[2]

[1]University of Florida, Gainesville, FL, US; [2]Duke University, Durham, NC, US

Background: Persistent production of HIV-1 by cellular reservoirs and chronic immune activation are major challenges in the elimination of infection and in the health of HIV-1 infected individuals. Monocyte derived macrophages (MDM) are significant contributors to continual viral production and chronic inflammation. HIV-1 infection of macrophages activates STAT1, STAT3 and STAT5. Infection also primes MDM rendering the cells hypersensitive to subsequent TLR stimulation. STAT5 has two functional binding sites in the HIV-1 LTR, although the effects of STAT5 activation on HIV-1 infection and immune responses by MDM are unknown. We tested the hypothesis that STAT5 activation supports HIV-1 infection and priming of MDM.

Methods: Human MDM or TZM-bl cells were treated with a STAT5 specific inhibitor or transfected with STAT5a/b siRNA prior to infection with replication competent HIV-1_{AD} or single cycle, luciferase-tagged HIV-1_{JRFL} envelope pseudotyped virus. Inhibition of STAT5 protein was verified by western blots. Infection was monitored by measuring supernatant p24 levels, luciferase enzyme activity, non-integrated *gag* and integrated HIV-1 copies. Cell surface expression of CD4 and CCR5 or intracellular p24 and TLR3, TLR4 or TLR7/8 induced TNF and IL-6 was determined by flow cytometry or ELISA.

Results: Pharmacologic inhibition or siRNA-mediated knockdown of STAT5 significantly reduced HIV-1 infection of MDM compared to control. Suppression of *de novo* or established infection by STAT5 inhibition was independent of changes in CD4 or CCR5 surface expression or number of non-integrated *gag* or integrated HIV-1 copies, but related to a significant reduction in HIV-1 LTR activity. STAT5 inhibition dramatically reduced TNF and IL-6 production mediated specifically through TLR7/8, but not through TLR3 or TLR4, in both infected and uninfected cells.

Conclusions: Our novel findings show a direct and indirect role for STAT5 in modulating HIV-1 infection in MDM. STAT5 directly support transcription of the viral genome, with no effect on host cell expression of CD4 or CCR5 and steps in the viral life cycle from entry through integration. STAT5 is involved in pro-inflammatory cytokine production induced by the TLR7/8 receptors, which sense ssRNA and viral infections, indicating an indirect role in HIV-1 infection. Disruption of TLR7/8 signaling mediated by STAT5 inhibition provides no apparent advantage for the virus. Thus, STAT5 is a key factor for HIV-1 replication and a novel anti-viral drug candidate.

184 Regulation of the Innate Immune Sensing of HIV by the Viral Capsid and the Cytosolic DNA Sensor cGAS

Nicolas Manel

Institut Curie, Paris, France

Background: Dendritic cells (DCs) play an important role in the detection of viral infections through innate sensing pathways and the induction of immune responses. The pathogenic virus HIV-1 escapes cytosolic innate immune sensing by monocyte-derived DCs. Innate sensing of HIV-1 by DCs can be rescued by complementing the virus with the small protein Vpx found in HIV-2, attributing the lack of cytosolic sensing of HIV-1 to to the poor ability of the virus to replicate in MDDCs as a result of the SAMHD1 restriction. In contrast, VSV-G-pseudotyped HIV-2 efficiently infects MDDCs and activates pathways of innate immunity. HIV-2 is much less pathogenic than HIV-1, suggesting that such recognition by DCs may be important for effective anti-HIV immune responses. However, the mechanism of cytosolic HIV sensing by DCs remained to be determined.

Methods: Initial experiments showed that the viral capsid and its interaction with the cellular protein Cyclophilin A plays an important role. To study HIV sensing, we designed mutations in capsid to increase its affinity for Cyclophilin A (HIVac).

Results: Strikingly, HIVac mutated viruses maintained the ability to activate DCs but had lost the ability to infect the DCs. Using such virus, we found that innate sensing requires synthesis of the viral cDNA, but not nuclear entry and genome integration. We also find that the wild-type HIV-1 capsid normally shields the cDNA before genome integration, preventing its detection by innate sensor(s). Finally, we examined cytosolic DNA sensors using RNAi. We find that the cytosolic DNA sensor cGAS (cyclic GMP-AMP synthase) is required for innate recognition of HIV-1 and HIV-2 cDNA by DCs.

Conclusions: Altogether, these results establish that cGAS is an important innate sensor of HIV-1 and HIV-2 and uncover an essential regulation of this sensing mechanism by capsid and Cyclophilin A. We are currently investigating various aspects of these innate immune mechanisms and new findings will be presented.

185 cGAS Induced Type I IFN Responses in Dendritic Cells From HIV Elite Controllers

Enrique Martin-Gayo[1]; Jacqueline Cronin[1]; Zhengyu Ouyang[1]; Taylor Hickman[1]; John Trombetta[2]; Florencia Pereyra[1]; Bruce Walker[1]; Alex Shalek[1]; Mathias Lichterfeld[3]; Xu Yu[1]

[1]Ragon Institute of MIT, MGH and Harvard, Boston, MA, US; [2]MIT Institute for Medical Engineering & Science, Boston, MA, US; [3]Massachusetts General Hospital, Boston, MA, US

Background: Cell-intrinsic HIV-1 immune recognition by IFI16 in CD4 T cells can cause pyroptosis, CD4 T cell loss, and increased immune activation. However, such cell-intrinsic immune responses in alternative cell subsets are thought to contribute to protective immune activity against HIV-1. Indeed, our previous studies indicated an accumulation of viral reverse transcripts and a rapid and sustained cell-intrinsic type I IFN response in primary conventional dendritic cells (cDC) from Elite controllers (EC) upon HIV-1 infection, which was functionally relevant for inducing and supporting effective HIV-1-specific CD8 T cell responses. However, molecular mechanisms accounting for such efficient cell-intrinsic immunity against HIV in cDCs from these patients remain unknown.

Methods: cDCs from EC, untreated chronic progressors (CP), HAART-treated and HIV-1 negative subjects were *ex vivo* infected with HIV-1, followed by assessments of expression changes of putative cytoplasmic DNA sensors. siRNA-mediated gene silencing was used to identify host factors responsible for the induction of cell-intrinsic immune responses. Single-cell RNA-Seq analysis of HIV-1-infected cDC was conducted to indentify gene expression pathways associated with cell-intrinsic HIV-1 immune recognition in cDC.

Results: Induction of IFN-I secretion in cDC depended on recognition of viral reverse transcripts by cGAS, but was largely unaffected by IFI16 or other known antimicrobial DNA sensors. RNAseq profiles obtained from single cDCs from EC infected with HIV-1 revealed the existence of distinct subpopulations of cells, characterized by differential expression of genes related to IFN signaling, immune activation, cytokine signaling and cellular metabolism, consistent with cell-intrinsic immune responses that are associated with improved stimulation of antigen-specific T cell responses.

Conclusions: Cell-intrinsic immune recognition of HIV-1 by cGAS in cDC induces type I IFN responses that initiate complex changes in gene expression profiles leading to functional maturation that can enhance antiviral immunity in elite controllers. These data suggest that cell-intrinsic immune recognition of HIV in CD4 T cells and in cDC can have distinct, and partially opposing functions in HIV-1 disease pathogenesis.

186 Characterization of Interferon-α Subtypes in the LPAC Model

Michael Harper[1]; Kathrin Gibbert[2]; Eric Lee[1]; Kejun Guo[1]; Stephanie Dillon[1]; Martin McCarter[3]; Ulf Dittmer[2]; Cara C. Wilson[1]; Mario Santiago[1]
[1]University of Colorado Anschutz Medical Campus, Denver, CO, US; [2]University of Duisburg-Essen, Essen, Germany; [3]University of Colorado Anschutz Medical Campus, Aurora, CO, US

Background: IFNα can inhibit acute HIV infection but is also associated with pathogenesis. The mechanism for this dual impact of IFNα remains unknown. There are 12 IFNα proteins but only one, IFNα2, has been used clinically. The IFNα subtypes are biologically distinct yet difficult to distinguish due to their high sequence similarity. Here we develop a method based on next-generation sequencing (NGS) to enumerate the relative abundance of different IFNα subtype transcripts. We then determined the relative potency of each IFNα subtype using the Lamina Propria Aggregate Culture model (LPAC), which recreates infection of the gut-associated lymphoid tissue (GALT), a major site of early HIV-1 replication.

Methods: Primer sets for quantitative PCR and Illumina NGS were designed in highly conserved regions that encompass polymorphic sites that can be used for IFNα subtype classification. Since plasmacytoid dendritic cells (pDCs) are the major producers of IFNα and likely migrate to the GALT during acute infection, total IFNα was quantified in RNA from pDCs that were negatively selected from PBMCs and exposed to cell-free R5-tropic HIV-1 (Ba-L) for 6 hours. Moreover, IFNα subtype distribution was determined in LPAC cells ± HIV-1. To determine the potencies of individual IFNα subtypes, each IFNα subtype was added to LPAC cells once at 400pg/mL immediately post-infection with HIV-Bal normalized to 10ng p24/mL. Productive infection was assessed using intracellular p24 flow cytometry and infectious virion release by TZM.bl assay at 4dpi.

Results: Negatively selected pDCs showed an average IFNα induction of >400-fold after 6hrs post HIV-1 exposure (n=5, p=0.0087). NGS analyses showed differential expression of IFNα subtypes in pDCs and LPAC cells co-incubated with HIV-1. In particular, IFNα5, IFNα8, and IFNα1/13 were overrepresented in multiple *ex vivo* conditions. In 2 donors tested so far, IFNα8 was the most potent in restricting productive HIV-1 infection and infectious virion release whereas IFNa16 was the least potent.

Conclusions: We developed a method for quantifying IFNα transcript production and the subtype distribution in primary cells. IFNα subtypes are not equally potent at inhibiting HIV-1. IFNα8 appears to be both highly expressed and the most potent at restricting HIV-1 in an *ex vivo* model of mucosal R5-tropic HIV-1 infection. The novel method presented here will be used to test if IFNα subtype expression profiles correlate with chronic immune activation in chronic HIV infection.

187 HIV Vpu Inhibits NF-kB Activity but Does Not Interfere With Interferon Regulatory Factor 3

Lara Manganaro; Elisa de Castro; Ana Maestre; Adolfo Garcia-Sastre; Ana Fernandez-Sesma; Viviana A. Simon
Icahn School of Medicine at Mount Sinai, New York, NY, US

Background: HIV accessory proteins have been shown to antagonize a number of different host innate restriction mechanisms. In particular, HIV Vpu counteracts the inhibitory effect of Tetherin on particle release and also hampers Tetherin mediated activation of the NF-κB pathway. The role of HIV Vpu in regulating the interferon response to infection by degradation of the Interferon Regulatory Factor 3 (IRF3) has, however, been subject of conflicting reports. We therefore, systematically investigated the expression of IRF3 in primary human CD4+ T cells and macrophages infected with different HIV strains. In addition we also tested the ability of Vpu to interfere with innate immune signaling pathways like NF-κB and IRF3 pathway.

Methods: Primary CD4+ T cells and primary macrophages from several healthy donors were infected with different viruses and the levels of IRF3 were determined by both western blot analysis and intracellular staining. To assess the ability of HIV Vpu to interfere with innate immune pathways, we transfected Vpu into 293T together with different NF-kB or IRF3 reporter plasmids. We used TNF-alpha and transfection of IKKb to selectively activate NF-κB and overexpression of TBK1 to induce IRF3.

Results: Here we report that HIV Vpu variants from different viruses fail to degrade IRF3 in infected primary T lymphocytes and macrophages. We first analyzed by Western Blot the levels of IRF3 in uninfected cells or infected with a HIV wild-type virus or HIV lacking Vpu. We did not observe any changes in IRF3 expression levels. We also used an intracellular staining approach to directly compare the levels of IRF3 at a single cell level in the infected and uninfected cell population. We found that the percentage of IRF3 positive cells in the HIV infected population versus the uninfected was comparable.

In addition, we observed that HIV NL4.3 Vpu had no effect on IRF3 dependent gene expression in reporter assays while it is able to down-modulated NF-κB dependent transcription downstream IKKb activation. Moreover all tested HIV-1 Vpus retained the ability to down-modulated NF-κB activity.

Conclusions: Using different approaches we show that HIV Vpu does not affect the of IRF3 protein expression levels in primary cells during infection. Moreover, we found that Vpu is able to downregulate NFKB but IRF3 dependent transcription. Taken together, these results suggest that HIV Vpu regulates antiviral innate response by only acting on the NF-κB pathway.

188 HIV-1 Exploits CD169 to Evade IFNα-Induced Antiviral State in Myeloid Cells

Hisashi Akiyama[1]; Nora Ramirez[1]; Gregory Gibson[2]; Simon Watkins[2]; Zandrea Ambrose[2]; Rahm Gummuluru[1]
[1]Boston University School of Medicine, Boston, MA, US; [2]University of Pittsburgh School of Medicine, Pittsburgh, PA, US; [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, US

Background: A hallmark of HIV-1 infection in vivo is chronic immune activation concomitant with type I interferon (IFN-I) production. Although IFN-Is induce an antiviral state in many cell types, HIV-1 can replicate even in the presence of IFN-Is in vivo. We have recently identified the IFN-I-inducible protein CD169 as an HIV-1 receptor on myeloid dendritic cells that can mediate robust infection of $CD4^+$ T cells in trans. Since CD169 expression is also induced by IFN-Is on macrophages, we hypothesized that CD169 induced by IFN-I could facilitate productive HIV-1 infection in macrophages in cis and thus offset antiviral effects of IFN-Is.

Methods: To investigate the effect of IFN-Is on HIV-1 replication in myeloid cells, a monocyte cell line, THP-1 or primary monocyte-derived macrophages (MDMs) were treated with IFNα for 48 hours and infected with HIVΔenv-luc reporter virus pseudotyped with HIV-1 Lai (HIV/Lai) or VSV-G (HIV/G) glycoproteins, or replication competent HIV-luc. HIV-1 fusion was measured by the conventional Vpr-BlaM assay. To investigate if $CD169^+$ myeloid cells are productively infected in vivo, lymph nodes (LNs) from pigtailed macaques chronically infected with $RT\text{-}SHIV_{mne027}$ were stained for $p27^{gag}$ and CD169.

Results: As reported previously, HIV/G infection was severely attenuated in IFN-treated-THP-1. Surprisingly, however, replication of HIV/Lai was enhanced in IFN-treated-THP-1 than in untreated THP-1. We found that HIV/Lai fusion was greatly enhanced in IFN-treated-THP-1, while that of HIV/G was severely attenuated. This enhanced fusion and infection depended on CD169 since pretreatment with αCD169 blocking antibody abrogated the enhancement of virus fusion and replication in IFN-treated-THP-1. IFNα treatment of MDMs

also up-regulated CD169 and HIV-1 fusion in treated MDMs was enhanced (2-fold) in a CD169-dependent manner. Interestingly, CD169 enhanced virus replication in MDMs even in the presence of IFNα (>2-fold higher compared to MDMs pretreated with αCD169 blocking antibody). Finally, LNs from SHIV-infected macaques showing signatures of immune activation contained more $CD169^+$ cells than those of uninfected animals and, intriguingly, a large proportion of $p27^{gag+}$ cells were also $CD169^+$.

Conclusions: These studies suggest that HIV-1 has exploited CD169 to attenuate IFN-I-induced antiviral state in myeloid cells.

189 Interferon-Induced Transmembrane Proteins (IFITMs) Antagonize Postintegration Replication of HIV but Are Overcome by Viral Membrane Accessory Proteins

Wingyiu Lee; Ifrah Omar; Richard D. Sloan

Queen Mary University of London, London, United Kingdom

Background: Interferon response triggered by acute HIV infection modulates the expression of genes in both infected and non-infected cells to control viral replication and virus spread. To date, a number of genes have been identified as host antiviral factors that interfere with various steps of the HIV replication cycle. Members of the interferon-induced transmembrane proteins (IFITMs) are induced in human macrophages and $CD4^+$ T cells upon upon exposure to interferons. While IFITMs have been shown to inhibit entry of HIV-1, the effects of IFITMs on other stages of the viral replication cycle are not known. Thus, we investigated the effects of IFITMs expression on the post-entry steps of the HIV replication cycle and how post-translational modification of IFITMs modulates these effects.

Methods: In transfection assays, wild-type or accessory gene-deleted HIV proviral DNA and expression vectors for IFITM1-3 were co-transfected into adherent HEK293T cells. In infection assays, HIV-1 viruses were made from transfected 293T cells and subsequently used to infect SupT1 cells that express human IFITMs upon exposure to doxycycline. Virus released from transfected or infected cells was quantified by p24 ELISA. Expression of viral proteins, IFITMs and other antiviral proteins were evaluated by immunoblotting or intracellular staining and flow cytometry. Quantitative PCR was used to measure the amount of total, multiply-spliced and singly-spliced viral RNA. Immunofluorescence and confocal microscopy were used to visualize IFITMs and viral components in cells.

Results: We show that expression of human IFITMs reduces the quantity of released HIV-1 viral particles produced in cells compared to vector controls. In the absence of the HIV accessory proteins Nef and Vpu, IFITM-mediated antagonism of HIV is more potent (20-30 fold). The reduction of viral output is caused by a decrease in synthesis of viral proteins independent of transcriptional control. While mutation of cysteine residues in IFITM1-2 that perturbs their palmitoylation and concomitant plasma membrane retention led to a reduction in all classes of viral RNA transcripts. This results in highly reduced HIV particle output by 10 to 100-fold compared to the wild-type IFITM1.

Conclusions: Our studies identify a novel role for IFITMs in controlling HIV replication at the post-transcriptional level and show that it is possible to engineer highly active anti-HIV IFITM variants by modulation of their palmitoylation status.

190 HSV-1-Induced Enhancement of HIV-1 Replication Is Dependent on Decrease in IFITM3 Levels

Viviane Andrade[1]; Milene Miranda[2]; Mario Stevenson[1]; Thiago M. Souza[2]

[1]University of Miami, Miami, FL, US; [2]Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

Background: The IFITM3 restriction factor has been described as a protein that impairs HIV-1 replication upon IFN induction. Since herpesvirus infections are extremely common in HIV-1-infected individuals and some HSV-1 proteins inhibit the IFN cascade, we analyzed whether HSV-1 could enhance HIV-1 replication by diminishing the levels of IFITM3.

Methods: Monocyte-derived macrophages were obtained from healthy donors and cells were infected with $HSV\text{-}1_{AR\text{-}29}$ (0.1 or 1 MOI) or co-infected with $HIV\text{-}1_{Ba\text{-}L}$ (10 ng/mL p24 antigen) during 2 or 14 days, respectively. To access HIV-1 quantification, we performed luciferase assay with infected TZM-BI from supernatants of infected-macrophages. The expression of IFITM3 was analyzed by immunoblotting with an anti-rabbit antibody against IFITM3. Knockdown of HSV-1 proteins was performed with siRNA against Us11 and VHS transcripts and further qPCR analysis to confirm knock down.

Results: Upon HIV-1-HSV co-infection, we observed a 3- 7 fold increase in HIV-1 production. At an HSV-1 MOI of 1,we observed a reduction in IFITM3 levels by 48 h post-infection. We analyzed changes in IFITM3 levels during the first 24 h of HSV-1 infection. Changes in IFITM3 occurred primarily at the late stages of HSV-1 infection. Treatment with ACV or IFN-2α prevented reduction of IFITM3, indicating that viral replication and ability to overcome IFN signaling are critical for IFITM3 modulation. To confirm that HSV-1 proteins produced at the late phase of replication are indirectly reducing IFITM3 levels by inhibiting the IFN cascade, Us11 and VHS was silenced. This was sufficient to prevent HSV-1-induced IFITM3 reduction. siRNA-mediated silencing of US11 and VHS also consistently prevented HSV-1-mediated enhancement of HIV-1 production.

Conclusions: Increased HIV-1 replication observed during HIV-1/HSV-1 co-infection is due to the production of Us11 and VHS by HSV-1. Upon inhibiting the IFN cascade, IFTM3 levels are reduced which contributes to an increased replication of HIV-1 in co-infected macrophages. Since co-infections are common in HIV-1 infected-individuals, our findings provide additional for exacerbation of HIV-1 replication in HSV-1/HIV-1 co-infected individuals.

191 Characterization of the Activity of an Innate Immunity Protein, the Apolipoprotein L6

Nitisha Pyndiah[1]; Angela Ciuffi[1]; Amalio Telenti[2]

[1]Institute of Microbiology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [2]J Craig Venter Institute, San Diego, CA, US

Background: Host restriction factors are proteins hampering virus replication, and share common features including positive selection, viral counteraction, interferon-inducible expression and differential expression among HIV+ patients. APOL6 was identified in a screen aiming at identifying novel HIV-1 candidate host restriction factors. Another member of the APOL family, APOL1, has been previously described for its protective role against the parasite *Trypanosoma brucei* and more recently as a new HIV restriction factor (Taylor *et al.,* 2013). The aim of the study was to characterize the activity of APOL6.

Methods: We evaluated the ability of APOL6 primate orthologues, chimeras and mutants to inhibit the GFP expression from an HIV-1 based genomic vector in co-transfection experiments. We also assessed the impact of APOL6 on transduction of reporter viruses. Analysis was carried out using flow cytometry

Results: APOL6-mediated restriction was validated in a co-transfection assay with an HIV-1 LTR-EF1-GFP, showing up to 10-fold reduced GFP expression in APOL6-expressing cells compared to control cells. Species-specific restriction of APOL6 primate orthologs co-transfected with HIV-1 LTR-EF1-GFP revealed a higher GFP inhibition mediated by hominids and new world monkey APOL6 compared to old world monkeys APOL6. A similar APOL6-mediated inhibition was observed when APOL6 was co-transfected with alternate GFP expression vectors. In contrast, APOL6 was not able to restrict HIV-based vector transduction nor adenovirus or LCMV. Furthermore, APOL1 and APOL3 constructs were also tested in co-transfection and transduction experiments and followed the same tendency as APOL6. Through co-transfection analyses using human and rhesus APOL6, respectively displaying high and low inhibition ability, we identified a specific APOL6 domain and residue mediating APOL6 effects.

Conclusions: All together, these data suggest that APOL6-mediated activity is not virus-specific, but rather displayed a broad action against various promoter constructs. This points out to a specific APOL6 mechanism, potentially acting at the level of nucleic acid (DNA or RNA) sensing and/or degradation. APOL6 domain and residue responsible for the activity was identified. The mechanism used by APOL6 is very likely to be shared by other members of the family. We are currently identifying APOL6 cellular interactants by Mass spectrometry to elucidate the mechanism of APOL6-mediated restriction.

192 HIV and SIV Inhibition by RNA-Associated Early Stage Antiviral Factor (REAF)

Aine McKnight
Queen Mary University of London, London, United Kingdom

Background: The interaction of viruses with their human host is a constant war. The discovery of novel anti-viral restriction factors illuminates unknown aspects of innate sensing and immunity.

Methods: An siRNA screen of ~20,000 human genes was used to uncover those involved in inhibition of HIV replication. We identified RNA-associated Early-stage Anti-viral Factor (REAF) as an inhibitor of HIV replication

Results: 114 genes were identified to be potentially involved in intrinsic resistance. Focusing on the most potent factors led us to REAF. REAF (previously RPRD2) was annotated in the human genome but with no known function. We observed more than 50 fold rescue of HIV-1 infection following knockdown of REAF by specific siRNA. Quantitative PCR was used to measure the effect of REAF knockdown on two steps in the replication cycle – production of reverse transcripts and integration of viral cDNA. Both steps were strongly enhanced. Conversely, when REAF is over expressed in target cells fewer reverse transcripts are produced. Human REAF can also inhibit HIV-2 and simian immunodeficiency virus (SIV) infection. REAF interacts (either directly or indirectly) with HIV RNA or RNA:DNA intermediates during reverse transcription. Also, during the process of reverse transcription REAF protein is degraded, within one hour of infection, in a proteosomal dependent manner.

Furthermore, REAF can inhibit HIV replication via different routes of entry into cells. Its potency is, however, highly dependent on the pathway of entry used and we show it is the lentiviral restriction factor 2 (Lv-2) [1,2].

Conclusions: We propose that REAF is part of an anti-viral surveillance system destroying incoming retroviruses. This novel mechanism could apply to invasion of cells by any intracellular pathogen.

1 Marchant, D., Neil, S. J., Aubin, K., Schmitz, C. & McKnight, A. An envelope-determined, pH-independent endocytic route of viral entry determines the susceptibility of human immunodeficiency virus type 1 (HIV-1) and HIV-2 to Lv2 restriction. *J Virol* **79**, 9410-9418, (2005).

2 Schmitz, C., Marchant, D., Neil, S. J., Aubin, K., Reuter, S., Dittmar, M. T. & McKnight, A. Lv2, a novel postentry restriction, is mediated by both capsid and envelope. *J Virol* **78**, 2006-2016, (2004).

193 Translational Control of APOBEC3G/F Restriction Factors by the HIV-1 Vif Protein

Camille Libre[1]; Santiago X. Guerrero[2]; Julien Batisse[1]; Roland Marquet[1]; Jean-Christophe Paillart[1]
[1]IBMC CNRS, Strasbourg, France; [2]Centre for Genomic Regulation, Barcelona, Spain

Background: The human immunodeficiency virus type 1 (HIV-1) requires the concerted contribution of many cellular factors to achieve efficient replication. Similarly, mammalian cells express a set of proteins called restriction factors to suppress viral replication. Among these factors, the family of APOBEC3 (Apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3 or A3) proteins and in particular A3G and A3F are the most efficient against HIV-1. They belong to a large family of cytidine deaminases that catalyze the deamination of cytidines to uridines in single stranded DNA substrate during HIV-1 retrotranscription and is lethal for the virus. The antiviral activity of A3G/F is counteracted by HIV-1 Vif (Viral infectivity factor) protein. Vif significantly reduces their expression in cell and their incorporation into viral particles by 1) recruiting an E3 ubiquitin ligase complex to induce their degradation by the proteasome, and 2) regulating their translation. Up to now, the mechanisms by which Vif regulates the translation of A3G/F are not known.

Methods: To address the role of Vif in the regulation of A3G/F translation, we tested the importance of the unstranslated regions (UTRs) of A3G/F mRNA in the translational inhibition. HEK 293T cells were transfected with wild-type and mutated constructions of A3G and A3F mRNAs (ΔUTRs, Δ5'UTR, Δ3'UTR and ΔSL) in presence or absence of Vif. These experiments were also performed with a proteasome inhibitor (ALLN) in order to distinguish the proteasomal degradation pathway from the translational inhibition.

Results: Although the translation of wild-type A3G/F mRNA is significantly reduced by Vif, we showed that the suppression of their 5'UTRs does not allow these mRNAs to be regulated by Vif anymore, suggesting that the 5'UTR is important for the translation repression. Next, we showed that the two distal stem-loops in the 5'UTR of A3G mRNA are crucial for the translational inhibition. Finally, we observed a strong correlation between the level of A3G/F protein translation in cell, their incorporation into viral particles, and the infectivity of released virions.

Conclusions: Experiments are in progress to identify with precision the mechanisms of A3G/F translational regulation and determine Vif domains involved in this process. Regulating the translation of A3G/F could thus be considered as a new target to restore a functional expression of A3G and viral restriction.

194 Evidence for Lentivirus-Driven Evolution of APOBEC3C

Cristina Wittkopp; Michael Emerman
Fred Hutchinson Cancer Research Center, Seattle, WA, US

Background: The Human APOBEC3 (A3) locus is a family of seven antiviral proteins on chromosome 22. Unlike A3D, A3F, A3G, and A3H, human A3C has little to no activity against HIV-1. However, we have previously found that for A3D and A3H, the homolog from other primates more potently blocks lentiviruses than the human version of these genes. Therefore, we hypothesized that A3C may potently restrict lentiviruses in non-human primates. To test this, we cloned A3Cs from several species and assayed for lentivirus restriction, and also performed evolutionary analyses to look for evidence of a virus-host arms race involving A3C.

Methods: We obtained A3C sequences from 12 primate species, and used the PAML software suite to perfom evolutionary analyses . Five of the A3C genes were cloned into expression vectors and their antiviral activity and sensitivity to Vif were functionally characterized. Antiviral activity was assessed by infectivity assays performed with HIV-1 and SIVagm in the absence of the viral antagonist, Vif. Sensitivity to Vif antagonism was assessed using infectivity assays with HIV-1 proviruses encoding Vifs from diverse lentiviruses. Cells were co-transfected with a provirus and each A3C or a vector control, and virions were harvested and used for infection. Virion and A3C protein expression were analyzed by Elisa and Western blot.

Results: A3Cs were functionally assayed for antiviral activity, and we found that in striking contrast to human A3C, several non-human primate A3Cs potently block HIV-1 and SIVagm (Vif deleted). In support of A3C being an active restriction factor, we found that A3C is evolving under positive selection. Futhermore, we identified rapidly evolving residues within A3:Vif binding domains, suggesting that activity against lentiviruses may drive the evolution of primate A3Cs. Preliminary evidence indicates that primate A3Cs have differential sensitivity to Vif antagonism.

Conclusions: Our functional and evolutionary data suggest that A3C is in genetic conflict with lentiviruses. The potent anti-lentiviral activity of several primate A3Cs, as well as the rapid evolution of residues important for Vif binding, indicate that A3C may play an important role in protecting primates from lentiviruses, but that human A3C has lost this activity. Thus, humans have lost the activity of an APOBEC3 antiviral gene that is present in other primates. We speculate that this lack of activity could impact our susceptibility to cross-species viral transmissions.

195 Reevaluation of the Role of the Small Host Cell GTPase Rab6 in the HIV-1 Replication Cycle

Isaac Zentner; Simon Cocklin

Drexel University College of Medicine, Philadelphia, PA, US

Background: The HIV-1 genome consists of only 9 genes and thus, depends highly on host cellular factors to replicate. Recent studies, through genome-wide siRNA screens, have identified many possible "HIV-1 dependency factors" HDFs. However, there lies a large inconsistency between these analyses and the majority of potential hits have not been verified in primary human target cells. Therefore, the goal of this proposal is to validate a recently identified possible HIV-1 Env-mediated host factor, Rab6A GTPase.

Methods: We utilized siRNA mediated knockdown in multiple cell lines and primary human monocyte-derived macrophages (MDMs) coupled with a HIV-1 single-round infection assay to define the mechanism by which this protein facilitates HIV-1 infection. Additionally, because Rab6A is ubiquitously expressed in two closely related isoforms, Rab6A and Rab6A', that have similar but distinct roles in the cell, both isoforms were investigated. Given that Rab6A is always cycling between active and non-active states, we examined the activity state needed for HIV-1 infection through dominant and constitutively active mutants of Rab6A, as well as knocking down the Rab6A-specific guanine nucleotide exchange factor (GEF), Ric1/Rgp1.

Results: siRNA knockdown of both isoforms of Rab6 in the U87 cell line confirmed its role in the viral replication cycle. Moreover, down regulation of both Rab6 isoforms in 293T cells used to generate virus demonstrated no effect on the overall production or infectivity of viruses, demonstrating that the protein facilitates processes only in the early stage of the replication. Contrary to previous reports, no dependency of the effect of knock down of Rab6 on the HIV-1 envelope was observed. Specific knock down of the individual isoforms, Rab6A and Rab6A', demonstrated that both were utilized by the virus but HIV-1 had a greater dependency upon Rab6A. Similar results were obtained with knockdown studies using primary human monocyte-derived macrophages. Diminishing Ric1/Rgp1 decreased infectivity revealing this Rab6A-specific GEF as an additional host factor for HIV-1.

Conclusions: Taken as a whole, these results demonstrate that Rab6 is co-opted by HIV-1 to facilitate a post entry step in the infection process and this is dependent on Ric1/Rgp1 activity. Further investigations may reveal a novel therapeutic pathway to combat HIV-1/AIDS, as well as help dissect the fundamental biological role of Rab6A(A/A') in primary human macrophages.

WEDNESDAY, FEBRUARY 25, 2015

Session P-A2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Nucleus Entry, Integration, and Export

196 The Mutated Form of Transportin 3 From Patients With Limb-Girdle Muscular Dystrophy 1F Hijacks Wild-Type Transportin 3 and Interferes With CPSF6 Subcellular Localization, Impairing HIV-1 Nuclear Entry

Sara Rodriguez-Mora[1]; Mayte Coiras[1]; Mercedes Bermejo[1]; Elena Mateos[1]; Ramon Marti[2]; Juan Jesus Vilchez[3]; Antonio Luis Andreu[2]; Jose Alcami[1]
On behalf of the AIDS Immunopathogenesis Unit

[1]*Instituto de Salud Carlos III, Madrid, Spain;* [2]*Vall d'Hebron Institut de Recerca, Barcelona, Spain;* [3]*Hospital Universitari i Politecnic La Fe, Valencia, Spain*

Background: Cells from patients with LGMD1F (limb-girdle muscular dystrophy 1F) show a point heterozygous mutation in *transportin 3* (*TNPO3*) gene. These cells expressed both TNPO3-wt and a mutated form with additional 15aa in the C terminus (TNPO3-mut). The interaction between TNPO3 and CPSF6 has been involved in HIV-1 decapsidation and transport of viral DNA to the nucleus, as well as in gene splicing. Our group described previously at HIV-1 pre-integration level was impaired in CD4+ T cells from LGMD1F patients. Now we have immortalized B lymphocytes from LGMD1F patients with the Epstein-Barr virus in order to characterize the mechanism of action of TNPO3-mut to thwart HIV-1 replication.

Methods: The interaction between TNPO3-wt and TNPO3-mut was analyzed in Jurkat E6-1 cells by co-transfection of tagged proteins along with pNL4-3_Renilla infectious clone. The level of expression of CPSF6 in LGMD1F cells and the role of TNPO3-mut in the viral splicing was analysed in B cells immortalized with Epstein-Barr virus from four patients with LGMD1F and two healthy relative controls. B cells were infected with a pseudotyped VSV-DEnv NL4-3_LUC virus.

Results: 1) Co-transfection of pNL4-3_Renilla in the presence of increasing concentrations of tagged TNPO3-mut proved that this form was interfering with HIV-1 replication in Jurkat E6-1 cells, likely due to the hijacking of TNPO3-wt, as was observed by immunoprecipitation. 2) Analysis by immunoblotting and immunofluorescence showed that LGMD1F cells had higher levels of the splicing proteins CPSF6 and SC35 in the nucleus, although the viral splicing was not affected.

Conclusions: HIV-1 replication was thwarted in LGMD1F cells due to the hijack of TNPO3-wt by TNPO3-mut, avoiding the translocation of HIV-1 DNA to the nucleus. As the entry of CPSF6 in the nucleus depends on TNPO3, the presence of TNPO3-mut was somehow inducing the accumulation of high levels of this splicing protein in the nucleus of LGMD1F cells, although the viral splicing was not affected in the immortalized LGMD1F B cells. More experiments would be necessary to determine whether TNPO3-mut is interfering with viral decapsidation through the inhibition of CPSF6 activity.

197 Longitudinal Epigenome-Wide Association Study of Pre- and Post-HIV–Infected Subjects

Sophie Limou[1]; George W. Nelson[1]; Elizabeth Binns-Roemer[1]; Jia Li[1]; Fathi Elloumi[1]; James J. Goedert[3]; Cheryl A. Winkler[1]

[1]*Frederick National Laboratory Operated by Leidos Biomedical Research, Inc, for the National Cancer Institute, Frederick, MD, US;* [2]*Frederick National Laboratory Operated by Leidos Biomedical Research, Inc, for the National Cancer Institute, Frederick, MD, US;* [3]*National Cancer Institute (NCI), Bethesda, MD, US*

Background: For nearly 25 years, extensive genetic and genomic association studies have revealed essential host factors for HIV control and disease progression, which notably led to the development of a new class of antiretroviral inhibitors (*CCR5-△32* association and CCR5 antagonists). Overall, the identified associations account for ~20% of the phenotypic variance suggesting that other factors are yet to be discovered. Epigenetic mechanisms are key regulators of gene expression that are not coded by DNA primary sequence and can impact complex diseases. Here, we evaluated for the first time whether HIV-1 infection modifies the host epigenome DNA methylation patterns.

Methods: We recruited 19 untreated HIV-infected individuals from the DC Gay cohort with longitudinal follow-up and PBMC samples available from pre-infection, early post-infection (<12 months), post-infection during clinical latency and post-infection at or near the inflection point. Following DNA and RNA extraction from the 80 PBMC samples, DNA was bisulfite-converted and genotyped with the Illumina Infinium HumanMethylation450 arrays, covering over 485,000 methylation sites across the genome. After normalizing the data, we compared the DNA methylation profiles of pre-infection *vs.* post-infection samples adjusting for batch effect, age, stage of infection and cell composition.

Results: Our preliminary analysis revealed that host genome DNA methylation profile is impacted by HIV-1 infection and highlighted several significantly differentially methylated sites ($P<10^{-7}$). Most genes where these differentially methylated sites are located have an immune-related function or were previously shown to interact with HIV-1 proteins (*MX1*, *TNFAIP8*, *PARP9*, and *IFI44L* genes in the top 5 hits).

Conclusions: We established a unique collection of samples representing pre-infection and post-infection timepoints, which allows for detection of DNA methylation changes within an individual and between individuals following HIV infection and during the HIV-1 infection course. This first epigenome-wide association study conducted in HIV-infected subjects has identified targets of epigenetic modifications by HIV. Our report indicates that the exploration of host epigenetic mechanisms opens a new promising avenue for discovery of critical host factors interacting with the virus that might be leveraged for translation to drug or vaccine development.

198 IN Variants Retarget HIV-1 Integration and Are Associated With Disease Progression

Frauke Christ[1]; Jonas Demeulemeester[1]; Zeger Debyser[1]; Rik Gijsbers[1]; Jan De Rijck[1]; Thumbi Ndung'u[2]; Paradise Madlala[1]
[1]*KU Leuven, Leuven, Belgium;* [2]*University of KwaZulu-Natal, Durban, South Africa*

Background: Distinct integration patterns of different retroviruses, including HIV-1, have puzzled virologists for over 20 years. A tetramer of the viral integrase (IN) assembles on the two viral cDNA ends, docks onto the target DNA (tDNA) to form the target capture complex (TCC) and catalyzes viral genome insertion into the host chromatin.

Methods: We combined structural information on the Prototype Foamy Virus TCC with conservation in retroviral IN protein alignments to determine aa-tDNA base contacts. We generated HIV-1 variants based on the observed variability at these positions, assessed replication capacities and performed integration site sequencing to reveal their integration preferences. Finally, we examined their effect on disease progression in a chronic HIV-1 subtype C infection cohort.

Results: We identified retroviral IN amino acids affecting molecular recognition in the TCC and resulting in distinct local tDNA nucleotide biases. These residues also determine the propensity of the virus to integrate into flexible tDNA sequences. Remarkably, natural polymorphisms IN_{S119G} and IN_{R231G} retarget viral integration away from gene dense regions. Precisely these variants were associated with rapid disease progression in a chronic HIV-1 subtype C infection cohort.

Conclusions: Our findings reveal how polymorphisms at positions corresponding to HIV IN_{119} and IN_{231} affect local as well as global integration site targeting. Intriguingly, these findings link integration site selection to virulence and viral evolution but also to the host immune response and antiretroviral therapy, since HIV-1 IN_{119} is under selection by HLA alleles and integrase inhibitors.

199 HIV-1 Integration Sites in Macrophages and CD4$^+$ T Cells Are Distinct

Yik Lim Kok; Valentina Vongrad; Mohaned Shilaih; Herbert Kuster; Roger Kouyos; Huldrych F. Günthard; Karin J. Metzner
University Hospital Zurich, Zurich, Switzerland

Background: The host genetic surroundings of integrated HIV-1 provirus have great impact on the activity of the HIV-1 LTR . Thus, HIV-1 integration site (IS) studies will contribute to the understanding of how to reactivate latent HIV-1 provirus, a currently pursued approach to eradicate the latent reservoir. Analysis of *in vivo* HIV-1 IS in macrophages is not feasible as it is too invasive to obtain them from HIV-1$^+$ patients. Moreover, IS analysis in monocyte-derived macrophages (MDMs) has only been done *in vitro* and was never compared to CD4$^+$ T cells within the same experimental settings. In this study, we compared and characterized HIV-1 IS in treated HIV-1$^+$ patients' MDMs and activated CD4$^+$ T cells infected *ex vivo* with the patients' autologous primary HIV-1 isolates.

Methods: 7 patients from the Zurich Primary HIV Infection study were selected based on the following inclusion criteria: (i) Successful viral suppression for ≥2 years and (ii) Efficient replication of autologous primary HIV-1 isolates in donors' MDMs. Patients' autologous HIV-1 and the clonal $HIV\text{-}1_{JR\text{-}FL}$ strain were used. HIV-1 IS were amplified with optimized non-restrictive linear amplification–mediated PCR, and sequenced using next generation sequencing technology. Sequencing reads were subjected to high quality trimming and mapped to the human genome. Gene clustering was done using the online bioinformatics tool DAVID. Fischer's exact test was used for statistical analysis.

Results: A total of 1160 unique HIV-1 IS were analysed. As expected, HIV-1 favours integration into introns of genes. However, autologous HIV-1 was less likely to integrate into introns of genes in MDMs compared to CD4$^+$ T cells ($p<0.01$). Significant difference was not observed between autologous HIV-1 and $HIV\text{-}1_{JR\text{-}FL}$ in MDMs for all genetic features examined. Consistently, analysis with DAVID showed that 37.5% versus 15.8% of enriched gene clusters (DAVID enrichment score≥1.3) in MDMs infected with $HIV\text{-}1_{JR\text{-}FL}$ and CD4$^+$ T cells infected with autologous HIV-1, respectively, overlap with those in MDMs infected with autologous HIV-1. Additionally, we have identified 12 genes in which at least 3 different HIV-1 IS are found between cell types and/or HIV-1 stains. 5 of these genes form an enriched cluster associated with catabolic processes and 3 have been found previously in clonally expanded CD4$^+$ T cells *in vivo*.

Conclusions: HIV-1 IS patterns between MDMs and CD4$^+$ T cells are distinct. Nonetheless, MDMs and CD4$^+$ T cells have common hotspots for HIV-1 integration.

200 A Screening for DNA Repair Enzymes That Affect HIV-1 Infection

Noriyoshi Yoshinaga[1]; Yusuke Matsui[1]; Keisuke Shindo[1]; shunichi Takeda[1]; Akifumi Takaori-Kondo[1]
[1]*Kyoto University, Kyoto-shi, Japan;* [2]*Kyoto University, Kyoto-shi, Japan*

Background: DNA repair enzymes might affect HIV-1 infection, as DNA intermediates of the virus play critical roles in the viral life cycle. Although several such molecules have been reported, interactions between HIV-1 and host DNA repair molecules have not been fully elucidated.

Methods: To screen for DNA repair enzymes that affect HIV-1 infectivity, a set of 33 DNA-repair-deficient DT40 cell lines with a single DNA repair gene deletion was tested for infectivity of VSV-G pseudo-typed NL4-3 with a luciferase reporter. To elucidate which steps in the viral life cycle candidate molecules function, late reverse transcription products, 2-LTR circle DNA, and integrated provirus were measured by quantitative PCR. To ask whether human RAD18 suppresses HIV-1 infection in human cells, knockdown of RAD18 by siRNA was applied to Jurkat cells and the virus infectivity was tested. To identify responsible domain of RAD18, over-expression of RAD18 wild-type, C28F, D221A or L274P was applied to 293T cells, and the virus infectivity was tested.

Results: HIV-1 infectivity in 8 of 33 DT40 cells was less than 50% of that in wild-type cells, suggesting the genes deficient in these cells might be required for efficient HIV-1 infection. On the other hand, the infectivity in Rad18 -/- cells was about 3-fold higher than that in wild type cells, suggesting Rad18 might inhibit HIV-1 infection. Quantitative PCR analyses showed that 4 of 8 DT40 cells with less infectivity accumulated 2-3 fold more 2-LTR circles and less than 50% integrated provirus, suggesting these genes might be required for efficient integration. In addition, Rad18 -/- cells accumulated about 5-fold more viral late RT product at 4h post-infection, suggesting Rad18 might inhibit reverse transcription. Jurkat cells that were transfected with siRNA for human RAD18 showed about 1.5-fold increase in HIV-1 infectivity when compared to cells transfected with a non-silencing control siRNA. Over-expression of RAD18 wild-typed, C28F RING domain mutant or C207F zinc-finger domain mutant in 293T cells inhibited HIV-1 infection, but that of L274P SAP domain mutant of RAD18 did not.

Conclusions: We have identified several candidate DNA repair genes that might support HIV-1 infection. We confirmed that RAD18 suppresses HIV-1 infection, and found that substitution of a DNA-binding residue lost this suppression. Our data support a model in which RAD18 inhibit reverse transcription by directly binding to viral DNA intermediates.

201 The Activity of HIV-1 Rev/RRE Varies Greatly Between Isolates

Patrick E. Jackson[1]; Denis Tebit[1]; David Rekosh[1]; Marie-Louise Hammarskjold[1]

[1]University of Virginia, Charlottesville, VA, US; [2]University of Virginia, Charlottesville, VA, US

Background: HIV replication is a highly regulated process, and the binding of the viral Rev protein to the Rev Response Element (RRE) is essential for the nucleocytoplasmic export of mRNAs that retain introns and thus for packaging of genomic RNA. Previous studies have shown that there is variation in Rev and RRE sequence both within and between patients. We previously assessed the activity of the Rev-RRE system in viruses isolated from patients. Variation of Rev/RRE function was observed between patients and within a patient as the infection progressed. In the present study, we sought to examine whether Rev/RRE functional variation could help to explain changes in the relative prevalence of HIV subtypes in populations.

Methods: A functional assay was developed, which utilizes an HIV vector system that packages HIV vector RNA into particles in a Rev-dependent fashion. The virus particles formed in this system transduce hygromycin resistance to target cells, allowing Rev/RRE activity to be read-out by counting the number of resistant colonies. Rev and RRE sequences can be tested in this system to measure the function of naturally occurring or artificial Rev-RRE pairs. Eight sequences were selected from the Los Alamos database representing two subtype A, four AG, and two G examples. Four subtype B patient isolates were also included.

Results: There was a 24-fold difference in functional activity between the most and least active naturally occurring Rev/RRE combinations (cognate pairs). There was no clustering within withsubtypes. When selected Rev and RRE sequences were tested with NL4-3 RRE and Rev, the absolute activity could not be predicted from the activity of the cognate pair. In a linear regression analysis, there was low correlation of RRE activity (R^2=0.32) but high correlation of Rev activity (R^2=0.95) with the functional activity of the original cognate pair.

Conclusions: Rev/RRE functional activity varied dramatically between naturally occurring cognate pairs. This functional variation appeared to be primarily driven by differences in Rev. The clinical significance of this finding is still unclear, but our results demonstrate that there are clear differences in the Rev activity of circulating viruses. This may play a role in viral fitness and replication dynamics and be reflective of immune pressure. Identification of the most efficient Rev/RRE combination would also likely be of use in optimizing lentiviral vector systems for gene therapy.

TUESDAY, FEBRUARY 24, 2015

Session P-A3 Poster Session — Poster Hall

2:30 pm – 4:00 pm

SAMHD1

202 A Surprising New Function of SAMHD1 as a Pro-Pathogenic Factor in HIV Infection

Gilad Doitsh; Nicole Galloway; Xin Geng; Isa Monus Arias; Zhiyuan Yang; Warner C. Greene

The J. David Gladstone Institute, University of California San Francisco, San Francisco, CA, US

Background: Depletion of CD4 T cells and development of chronic inflammation are signature processes in HIV pathogenesis that propel disease progression. Due to endogenous SAMHD1 restriction activity in quiescent lymphoid CD4 T cells, the viral chain elongation phase of reverse transcription is attenuated, giving rise to incomplete cytosolic DNA transcripts. CD4 T-cell death is triggered after sensing of these cytosolic DNA intermediates by interferon gamma Inducible protein 16 (**IFI16**). Death occurs following caspase-1 activation in inflammasomes and the induction of **pyroptosis**, a highly inflammatory form of programmed cell death. These findings mechanistically connect CD4 T-cell death and chronic inflammation––the two signature pathogenic processes of active HIV infection.

Methods: Human lymphoid aggregated cultures (HLACs) prepared using tonsil and spleen, and lymph node biopsies from consenting HIV-infected volunteers were used.

Results: We now show that SAMHD1 restriction activity influences how CD4 T cells die. Degradation of SAMHD1 by Vpx encoded by HIV-2 thwarts abortive infection in resting, non-permissive lymphoid CD4 T cells redirecting the cell death pathway away from caspase-1-mediated pyroptotic pathway (inflammatory) toward caspase-3-mediated apoptotic pathway (noninflammatory). SAMHD1 effectively suppresses caspase-1 activation and pyroptosis when infection occurs with cell-free virions. However, in the context of cell-to-cell transmission, which is 100-1,000-fold more efficient, SAMHD1 restriction is only partially effective resulting in the accumulation cytoplasmic viral DNA. This DNA is sensed by IFI16 resulting in caspase-1 activation and triggering of the pyroptotic death pathway. The action of other cellular factors like TREX1 and SLX4 (single and double strand DNA nucleases) may require further increase in the levels the cytosolic DNA needed to trigger pyroptosis.

Conclusions: 1. The Vpx protein thwarts inflammatory pyroptosis following HIV-2 infection by degrading SAMHD1 thereby avoiding abortive infection and sensing of cytosolic viral DNA.

2. SAMHD1 is a bifunctional host factor capably restricting infection of resting CD4 T cells by cell-free HIV virions but functioning as a pro-pathogenic factor when resting CD4 T cells are infected by HIV-1 by the cell-to-cell route.

203 Mapping Vpx and Vpr Specificity in Antagonism of SAMHD1

Chelsea Spragg; Michael Emerman

Fred Hutchinson Cancer Research Center, Seattle, WA, US

Background: The lentiviral accessory protein Vpx enhances infectivity of macrophages, dendritic cells, and resting T-cells by inducing degradation of the restriction factor SAMHD1, which blocks replication at reverse transcription. Vpx bridges SAMHD1 to the host ubiquitin ligase substrate receptor DCAF1, leading to polyubiquitination of SAMHD1 and degradation by the proteasome. The *vpx* gene is present in only two major lineages of lentivirus including HIV-2, but the paralagous *vpr* is present in all extant lineages. In certain cases, Vpr also has the ability to degrade host SAMHD1. SAMHD1 has evolved under positive selection due to viral antagonism, resulting in species-specificity between host SAMHD1 and viral Vpx/r. Depending on the lineage, Vpx exclusively targets either the N-terminus or the C-terminus of SAMHD1; however, the regions of Vpx/r controlling specificity are unknown. The structure of SIVmac Vpx bound to DCAF1 and the C-terminus of SAMHD1 has been solved, but there is extreme sequence diversity in *vpr* and *vpx* from divergent viruses.

Methods: We used an evolutionary and structural approach to find appropriate and robust breakpoints in Vpx and Vpr in order to create functional, chimeric viral proteins. By assaying for the gain of ability to degrade resistant SAMHD1, these chimeric proteins assisted in mapping of determinants of specificity in Vpx and Vpr from several lentiviral lineages.

Results: We found that the majority of residues involved in binding DCAF1 were conserved in essentially all SAMHD1-degrading Vpx and Vpr. We identified highly conserved amino acids flanking the regions of SIVmac Vpx involved in binding SAMHD1. These conserved motifs served as breakpoints to create chimeric proteins between Vpr and Vpx from SIVs infecting macaque, red-capped mangabey, and African green monkeys. We were then able to retarget Vpx and Vpr from different lentiviruses to degrade heterologous SAMHD1. Depending on the lineage, the specificity of Vpx/r in degrading SAMHD1 maps to one or two regions in the viral protein.

Conclusions: The structure of Vpx and Vpr proteins and their interaction with the host ubiquitin ligase is widely conserved, despite high levels of sequence variation across lineages. Given the evolutionary constriction in maintaining this ubiquitin ligase binding, similar regions of Vpr/x are used to target SAMHD1, allowing the mapping of sites that govern SAMHD1 antagonism in species-specific interactions.

204 Differentiation Stimuli Strongly Impact the Ability of Macrophages to Support HIV-1 Replication Due to SAMHD1 Restriction

Ester Ballana[1]; Roger Badia[1]; Eva Riveira-Muñoz[1]; Alba Ruíz[1]; Javier Torres-Torronteras[2]; Bonaventura Clotet[1]; Eduardo Pauls[1]; Ramon Marti[2]; José Esté[1]
HIV Pathogenesis Research Group
[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain; [2]Institut de Recerca Hospital Universitari Vall d'Hebron, Barcelona, Spain

Background: Macrophages are a highly heterogenic cell population with cellular properties strongly influenced by the factors present during differentiation. Monocytes are refractory to HIV infection and only become susceptible to infection after differentiation, due to deactivation of the restriction factor SAMHD1 by phosphorylation. We have shown that SAMHD1 deactivation is controlled by cyclin-dependent kinases (CDK), which in turn, control cell activation and proliferation. Here, we used human primary monocyte-derived macrophages (MDMs) differentiated under different conditions to evaluate cell activation and proliferation, differential gene and protein expression patterns and susceptibility to HIV-1 infection.

Methods: CD14+ monocytes were differentiated with M-CSF or GM-CSF to generate M-CSF (M-MDM) or GM-CSF-induced MDM (GM-MDM). Expression of cell surface antigens and cell activation and proliferation markers was evaluated by flow cytometry. Susceptibility to HIV-1 infection was examined by flow cytometry after infection with a VSV-pseudotyped NL4-3 GFP-expressing virus in the presence or not of drugs targeting HIV or inhibiting cell activation or proliferation. SAMHD1 restriction was bypassed by VLP-containing Vpx. Gene expression was assessed by quantitative PCR and protein expression and phosphorylation by immunoblotting. dNTP levels were determined using a polymerase-based method.

Results: MDMs displayed different morphological characteristics dependent on the differentiation conditions, but no significant differences in cell surface antigens expression were observed. M-MDM were roughly 10-fold more susceptible to HIV-1 infection than GM-MDM, which correlated with higher dNTP levels in M-MDM compared to GM-MDM (from 3 to 80 fold difference depending on the nucleotide, being dCTP the lowest and dTTP the highest). Although no differences were found in SAMHD1 expression, a change in SAMHD1 activation was observed, as a consequence of different cell activation. Degradation of SAMHD1 by Vpx increased HIV replication in both cases, minimizing the original differences in susceptibility. Accordingly, SAMHD1 degradation led to an increase in dNTP intracellular levels under both conditions.

Conclusions: Differentiation strongly impacts the ability of MDMs to support HIV-1 replication, mainly due to SAMHD1 function determined by cell activation differences. These resultst suggest that the choice of macrophage model is important for evaluation of virus-cell interactions during HIV infection.

205 Essential Role of Cyclin D3 in dNTP Pool Control and HIV-1 Replication in Macrophages

Ester Ballana[1]; Alba Ruíz[1]; Eduardo Pauls[1]; Javier Torres-Torronteras[2]; Roger Badia[1]; Eva Riveira-Muñoz[1]; Bonaventura Clotet[1]; Ramon Marti[2]; José Esté[1]
HIV Pathogenesis Research Group
[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain; [2]Institut de Recerca Hospital Universitari Vall d'Hebron, Badalona, Spain

Background: Cyclins control the activation of cyclin-dependent kinases (CDK), which in turn, control cell proliferation. We have shown that the virus restriction factor SAMHD1 is controlled by CDK6, a CDK controlling early G0 to G1 transition of the cell cycle. However, the cyclin controlling the process of SAMHD1 function has not been clearly identified in primary cells.

Methods: Monocytes were isolated and transfected with siRNA against different cyclins controlling cell cycle. Transfected monocytes were differentiated in macrophages using M-CSF. RNA interference was assessed by quantitative PCR and Western blot. Primary monocyte-derived macrophages (MDM) were infected with a VSV-pseudotyped NL4-3 GFP-expressing virus or full-replicative R5 HIV-1 strain BaL. Total viral DNA formation was quantified by qPCR and HIV replication measured by flow cytometry. SAMHD1 phosphorylation and protein expression were analyzed by immunoblotting. dNTP intracellular levels in siRNA-treated MDM were determined using a polymerase-based method.

Results: RNAi of eight distinct cyclins led to efficient and specific downregulation (up to 90% efficacy) of the corresponding cyclin as compared to mock-transfected cells or cells transfected with a non-targeting siRNA in MDM. Downregulation of the CDK6-associated cyclin D3 showed the strongest inhibitory effect ($p=0.0002$) of HIV-1 replication and total viral DNA formation in acutely infected MDM. Cyclins D1 and E2 (associated to CDK6 and CDK2, respectively) had a lower inhibitory effect. Cyclin A2, B1, B2 and D2 did not block HIV-1 replication. Alternative siRNA sequences targeting cyclin D3 confirmed the effect of cyclin D3 in HIV-1 infection and total viral DNA formation. Cyclin D3 downregulation led to a significant ($p<0.01$) reduction of SAMHD1 phosphorylation (at residue T592), CDK2 activation as measured by phosphorylation of T160 and decreased intracellular dNTP levels. The effect of cyclin D3 RNA interference was lost after degradation of SAMHD1 by HIV-2 Vpx.

Conclusions: Knockdown of cyclin D3 has a major impact in SAMHD1 phosphorylation, dNTP levels and HIV-1 reverse transcription and replication. Cyclin D3 is the catalytic partner of CDK6. Thus, our results indicate a fundamental role of the CDK6-cyclin D3 complex in SAMHD1-mediated virus restriction during G0 to G1 transition. Agents targeting cell proliferation may prevent new rounds of infection and hypothetically, might prevent the proliferation of persistently infected cells.

206 Low SAMHD1 Expression Renders Activated and Proliferated CD4$^+$ Susceptible to HIV-1

Nabila Seddiki[1]; Nicolas Ruffin[1]; Vedran Brezar[1]; Diana Ayinde[2]; Julian Schulze zur Wiesch[3]; Jan van Lunzen[3]; Olivier Schwartz[2]; Jean-Daniel Lelièvre[1]; Jacques Banchereau[1]; Yves Lévy[1]
[1]Inserm U955 Eq16/UPEC, Créteil, France; [2]Institut Pasteur, Paris, France; [3]University Medical Center, Hamburg-Eppendorf and Heinrich-Pette-Institute, Hamburg, Germany

Background: HIV-1 replication depends on the state of cell activation and division. It is established that SAMHD1 restricts HIV-1 infection of resting CD4$^+$ T cells. The modulation of SAMHD1 expression during T-cell activation and proliferation however remains unclear, as well as a role for SAMHD1 during HIV-1 pathogenesis.

Methods: SAMHD1 expression was assessed in CD4$^+$ T cells *ex vivo*, after their activation and *in vitro* HIV-1 infection. We performed phenotype analyzes and functional studies using CD4$^+$ T cells from peripheral blood and lymph nodes from cohorts of HIV-1 infected subjects under anti-retroviral treatment or not, and controls.

Results: We show that SAMHD1 expression decreased during CD4$^+$ T cell proliferation in association with an increased susceptibility to *in vitro* HIV-1 infection. Additionally, circulating memory CD4$^+$ T cells are enriched in cells with low levels of SAMHD1. These SAMHD1^{low} cells are highly differentiated, exhibit a large proportion of Ki67$^+$ cycling cells and are enriched in Th17 cells. Importantly, memory SAMHD1^{low} cells were depleted from peripheral blood of HIV-infected individuals. We also found that lymph node follicular helper T (Tfh) cells lacked the expression of SAMHD1, which was accompanied by a higher susceptibility to HIV-1 infection *in vitro*.

Conclusions: We demonstrate that SAMHD1 expression is decreased during $CD4^+$ T cell activation and proliferation. Also, $CD4^+$ T-cell subsets known to be more susceptible to HIV-1 infection, e.g. Th17 and Tfh cells, display lower levels of SAMHD1. These results pin point a role for SAMHD1 expression in HIV-1 infection and the concomitant depletion of $CD4^+$ T cells.

207 SAMHD1 Partially Blocks Lentiviral Gene Transfer Into Hematopoietic Stem Cells

Duo Li[1]; Erika Schlaepfer[1]; Annette Audigé[1]; Baek Kim[2]; Roberto Speck[1]
[1]*University Hospital Zurich, Zurich, Switzerland;* [2]*Department of Pediatrics Emory School of Medicine, Atlanta, GA, US*

Background: Understanding how to achieve efficient transduction of hematopoietic stem cells (HSCs), while preserving their self-renewing capacity, is key for applying lentivirus-based gene engineering methods in Phase I/II clinical trials. The sterile alpha motif (SAM) domain and HD domain-containing protein 1 (SAMHD1) was recently identified as a HIV-1 restriction factor in myeloid cells and resting $CD4^+$ T cells that interferes with reverse transcription by decreasing the nucleotide pools or by its RNase activity. HIV-2 and SIV have evolved to counteract the effects of SAMHD1 by their accessory protein Vpx, which targets SAMHD1 for proteasomal degradation. We hypothesized that SAMHD1 also interferes with HIV-1 vector-based HSCs transduction.

Methods: Expression of SAMHD1 in HSCs was quantified by western blotting and real-time quantitative PCR (qPCR). For HSCs transduction, we used HR-GFP-Vpx-/+ lentivirus, which carries Vpx and encodes GFP. Integrated provirus and viral DNA intermediates in HSCs and monocyte-derived macrophages (MDMs) were quantified by qPCR. Transduction efficiency was assessed by flow cytometry.

Results: Our results show that SAMHD1 is highly expressed in HSCs already at 2 hours culturing in a medium enriched with cytokines conventionally used for transduction of HSCs. In contrast, fresh HSCs have poor SAMHD1 expression. Expression levels of SAMHD1 in cultured HSCs are comparable to those found in MDMs. Following lentiviral based transduction with HR-GFP-Vpx+, we did not observe any increase of proviral DNA in HSCs while there was a significant one in MDMs which served as positive control for the assay. Similarly, there was a less than 3-fold increase of DNA intermediates in HSCs a vigorous one in MDMs. HSCs exposed to HR-GFP-Vpx+ showed a minor but significant increase in the number of GFP^+ cells which was associated with a decrease in SAMHD1 expression. GFP^+ cells were detected mostly within the population of cells containing low amounts of SAMHD1. There was an significant increase of the percentage of $GFP^+SAMHD1^-$ cells, while $GFP^+SAMHD1^+$ cells decreased 7 days post infection when compared to cells exposed to HR-GFP-Vpx- viral like particles.

Conclusions: HSCs cultured in cytokine-enriched medium, unlike uncultured cells, express high levels of SAMHD1. Vpx-mediated decreases of SAMHD1 expression levels enhances transduction rate in a minor sub-population of HSCs. The data imply that blocks mainly at cell entry are the major limiting step for efficient transduction.

THURSDAY, FEBRUARY 26, 2015

Session P-A4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Enhancers and Inhibitors of Viral Infectivity and Entry

208 Fresh Semen Harbors HIV-Enhancing Amyloids and Decreases the Efficacy of Microbicides

Jan Munch[3]; Onofrio Zirafi[3]; Shariq Usmani[3]; Kyeong-Ae Kim[3]; Frank Kirchhoff[3]; Christopher D. Pilcher[1]; Haichuan Liu[1]; H. Ewa Witkowska[1]; Warner C. Greene[2]; **Nadia R. Roan**[1]
[1]*University of California San Francisco, San Francisco, CA, US;* [2]*The J. David Gladstone Institutes, San Francisco, CA, US;* [3]*Ulm University Medical Center, Ulm, Germany*

Background: Semen, the most common vehicle for HIV transmission, enhances HIV infection *in vitro*. Previously, naturally-occurring peptides derived from the semen proteins prostatic acid phosphatase (PAP) and semenogelin (SEM) were shown to assemble into amyloid fibrils that markedly enhance HIV infection. Here, we investigated whether fresh semen samples contain these amyloids and affect the antiviral efficacy of various classes of microbicides.

Methods: Confocal microscopy, electron microscopy (EM), atomic force microscopy (AFM), quantitative mass spectrometry, ELISAs, and infection assays were used to detect, quantitate, and characterize endogenous HIV-enhancing amyloids in semen and to determine how semen affects the efficacy of microbicides.

Results: Endogenous PAP and SEM amyloids were detected in unmanipulated semen by immunogold EM, confocal microscopy, and AFM. These amyloids are present in semen from uninfected and HIV-infected individuals and directly bind HIV virions. The endogenous levels of these amyloidogenic fragments correlated significantly with the HIV enhancing activity of the semen samples, suggesting that they may be responsible for the ability of semen to enhance HIV infection. We also found that semen reduced the antiviral efficacy, by 10 to 20-fold, of multiple classes of antiretrovirals (ARVs) including neutralizing antibodies, NRTI's and NNRTI's, and inhibitors against Integrase and Protease. In striking contrast, semen deficient in amyloids did not enhance HIV infection or impair the antiviral activity of these ARVs. Notably, the sole microbicide that retained full activity in the presence of semen was Maraviroc (MVC), an HIV entry inhibitor that was the only microbicide investigated which targeted a host component instead of the virus itself.

Conclusions: Our results demonstrate that amyloids are abundant in fresh semen and that the ability of semen to enhance HIV infection markedly impairs the activity of microbicides targeting viral components. In contrast, MVC, which targets the cellular CCR5 entry cofactor, retained full activity in the presence of semen. Thus, compounds targeting cellular components may be advantageous for microbicide development. Our results may explain why most microbicides largely failed in clinical trials and suggest that inclusion of compounds that antagonize seminal amyloids will greatly enhance the efficacy of antiretroviral microbicides.

209 Semen's HIV Enhancing Activity Is an Individual Characteristic Independent of VL

Christopher D. Pilcher; Teri Liegler; Jason Neidleman; H. Ewa Witkowska; Wendy Hartogensis; Kara Marson; Peter Bacchetti; Frederick M. Hecht; Warner C. Greene; Nadia R. Roan
University of California San Francisco, San Francisco, CA, US

Background: Semen enhances HIV infection *in vitro*, and semen-derived amyloids made up of a peptide from the abundant protein semenogelin 1 (SEM1) are sufficient to mediate this activity. We sought to compare the infectivity-enhancing activity of semen among HIV infected men, and examine its relationship to concentrations of amyloidogenic peptides.

Methods: We studied 188 paired seminal and blood plasma samples from 113 individual UCSF Options study subjects at least four months after acute HIV infection. 20 subjects were studied at multiple timepoints prior to ART; 20 were studied before and after suppressive ART and 20 before and after ART interruption. Quantitative mass spectrometry and ELISAs were used to quantify amyloidogenic SEM peptide fragments. Semen-mediated enhancement of HIV infection was measured by mixing serial dilutions of each sample with HIV prior to adding it to TZM-bl reporter cells, and assessing infection levels by luminescence 3 days later. Seminal fluid VL was quantified using Abbott RealTime PCR.

Results: Semen from HIV infected men enhanced HIV infectivity (mean 10.8-fold, range from 0- to >35-fold enhancement). Levels of endogenous amyloidogenic SEM were correlated with the infectivity-enhancing activity of semen samples (r=0.48;p<.0001). For individual subjects with longitudinal samples, levels of both infectivity enhancement and SEM tended to be similar over time (intraclass correlations (ICCs) for infectivity enhancement 0.33, SEM 0.49, semen VL 0.42). Infectivity enhancing activity of semen had little association with ART naïve semen VL (r=-0.08). With interruption of ART (baseline semen VL<200 cp/mL in 18/20 subjects), there was no systematic increase in either infectivity enhancement (mean 18% decrease, p=0.17) or SEM (mean 13% decrease, p=0.054).

Conclusions: Our results suggest that semen from HIV infected men can enhance the efficiency with which HIV infects permissive cells, in a manner that persists in men taking ART and is independent of semen VL but is directly associated with levels of amyloidogenic SEM fragments. The HIV-enhancing activities of multiple semen samples from the same individual were relatively similar, even upon ART treatment, suggesting that the HIV enhancing activity of semen can be considered an individual characteristic. Together, these data suggest that individual semen characteristics other than HIV VL may be important factors in HIV transmission.

210 Hyaluronan Reduces HIV Infection of CD4+ T Cells and Greatly Enhances HIV Inhibition by Tenofovir

Peilin Li; Katsuya Fujimoto; Lilly Bourguignon; Steven Yukl; Steven Deeks; Philipp Kaiser; Peggy Kim; Diane Havlir; Harry Lampiris; Joseph K. Wong
University of California San Francisco, San Francisco, CA, US

Background: Better strategies are needed to prevent mucosal transmission of HIV. The major extracellular matrix receptorCD44, present on virion and target cells, has been reported to strongly influence viral infectivity. Topical formulations of antiviral drugs like tenofovir (TDF) are being studied in HIV prevention. We investigated how the natural ligand of CD44, hyaluronan, modulates HIV infection in vitro when used alone or with TDF.

Methods: HIV stocks were produced with or without CD44. Infection of cell lines (M7 Lue, TZM-bl) and of primary CD4+ T cells were performed with or without exogenous HA, inhibitors to HA signaling through PKCa, and TDF. Infection was gauged by RLU and p24 measurements. IC50 and IC95 of TDF were calculated. Significance was tested using a T-test.

Results: HA reduced HIV infectivity only when virions expressed CD44. HA inhibited HIV infection modestly and consistently in a dose dependent manner and removal of endogenous HA enhanced viral infectivity. Treatment with Gö6976, an inhibitor of PKCa, abrogated the effects of HIV to a degree similar to exogenous HA. Notably, co-treatment of cells with HA and tenofovir shifted TDF IC50 by greater than 1 log compared to TDF alone, while TDF IC95 was reduced by over 400 fold in the presence of HA. Similar findings were seen with R5 and X4 virus. HA was synergistic with the entry inhibitor T20 but to a lesser degree.

Conclusions: HA interacts with CD44 on virion and cell membranes to modulate HIV infection at the early (binding, entry) and post entry steps in the viral lifecycle. We found marked enhancement of antiviral effects of TDF by HA. Manipulation of CD44-HA interactions, used alone or together with antiviral drugs, deserves further study as a novel strategy to prevent transmission.

211 Alpha-defensins increase HIV transcytosis: role in STI-mediated enhanced HIV transmission

Kimyata B. Valere[1]; Aprille Rapista[1]; Alison Quayle[2]; Wuyan Lu[3]; Eliseo Eugenin[1]; Theresa Chang[1]
[1]Rutgers University-New Jersey Medical School, Willingboro, NJ, US; [2]University Health Science Center, New Orleans, LA, US; [3]University of Maryland School of Medicine, Baltimore, MD, US

Background: Although mucosal epithelial cells provide the first-line of defense against HIV infection, HIV can cross the genital or intestinal epithelium by transcytosis. The risk of HIV transmission is increased in individuals with Sexually Transmitted Infections (STIs). Defensins are antimicrobial peptides important for mucosal innate immunity. Alpha-defensins, including human defensin 5 (HD5) and human neutrophil defensins 1-3 (HNPs1-3), are elevated at the genital mucosa in individuals with STIs. HD5 promotes HIV infectivity and contributes to enhanced HIV infection by STIs in vitro. Unlike HD5, HNPs exhibit anti-HIV activity in vitro. However, enhanced HIV acquisition is associated with increased levels of HNPs in cervicovaginal fluid. In this study, we examined the effect of alpha-defensins on epithelial integrity and the subsequent impact on HIV transcytosis in polarized epithelial cells.

Methods: Defensins were added to the apical side of polarized intestinal epithelial (Caco) cells. Transepithelial electrical resistance was measured by cellZscope to monitor epithelial permeability. Distribution of tight junction markers was observed by immunofluorescent staining of ZO-1 or occludin. To examine HIV transcytosis, HIV-1_{BAL} was added to the apical side of polarized epithelial cells, and HIV that crossed to the basolateral side was measured by HIV p24 ELISA.

Results: HNP significantly increased epithelial permeability in a dose-dependent manner within 4 hours, suggesting transient HNP1-mediated epithelial disruption. However, HD5 at high concentrations slightly reduced TERs. Linear analogs of HNP1 and HD5 did not affect epithelial permeability, indicating that the impact of alpha-defensin on epithelial integrity is structure-dependent and not charge-dependent. Interestingly, both HD5 and HNP1 caused discontinuation and internalization of tight junction proteins in Caco cells. In agreement with their impact on epithelial permeability, HNP1, but not HD5, significantly increased HIV transcytosis in polarized intestinal epithelial cells.

Conclusions: Our results demonstrated that HNP1 and HD5 displayed distinct functions in facilitating transmission of HIV. Since HNP1 can alter the integrity of the mucosal epithelium leading to increased HIV transcytosis, defensin-mediated disruption of mucosal barriers offers a window of opportunity for HIV to invade the host. Our study provides a new role of HNP1 in STI-mediated enhancement of HIV transmission.

212 The Design and Investigation of Mechanism of Novel Potent HIV-1 Entry Inhibitor SC12

Marina Tuyishime; Simon Cocklin
Drexel University College of Medicine, Philadelphia, PA, US

Background: The process of HIV-1 entry is key to the replication of the virus and viral Env serves as a hot target as a first protein complex encountering the target cell. We designed a novel potent HIV-1 entry inhibitor, SC12 that binds viral Env and prevents the infection. In addition, SC12 has better predicted ADME/PK (absorption, distribution, metabolism and excretion/pharmacokinetic) properties compared to the lead chemotype in HIV-1 entry field, BMS compounds. Given the enormous potential of the small molecule entry inhibitor, SC12, we sought to investigate the mechanism of its action against HIV-1 viruses.

Methods: We utilized the single-round infection assay against HIV-1 viruses pseudotyped with HIV-1 Env and AMLV Env to identify the potency and specificity of SC12. Surface Plasmon Resonance (SPR) was employed to determine the binding site of SC12 on viral Env and to investigate its potential to block sCD4-gp120 binding. We designed a novel attachment assay based on the temperature dependence of entry to determine the effect of SC12 on viral attachment and viral fusion.

Results: SC12 has low nM to mid μM potency range against numerous isolates of HIV-1 clades A through D. In addition, SC12 was determined to directly bind gp120 and the gradual increase of SC12 concentration did not affect sCD4 binding to gp120. Moreover, SC12 did not block viral attachment to the cells regardless the time of the addition of the compound: before, after or at the time of the viral infection.

Conclusions: We have designed a novel small molecule inhibitor that is potent against various HIV-1 isolates proposing that the binding site of SC12 is conserved throughout the clades. We did not observe a concentration-dependent competition of SC12 and sCD4 for the binding site on gp120, proposing that SC12 is not an attachment inhibitor. Moreover, at the concentration of 70nM SC12 did not affect viral attachment to the cells, however, was able to inhibit over 50% of viral infectivity. Taken together, we propose that SC12 is not

an attachment inhibitor and blocks viral infection by other mechanism. The further characterization of its mechanism of action and optimization of SC12 will yield important basic information about the process of HIV-1 entry and potentially lead to the novel therapies.

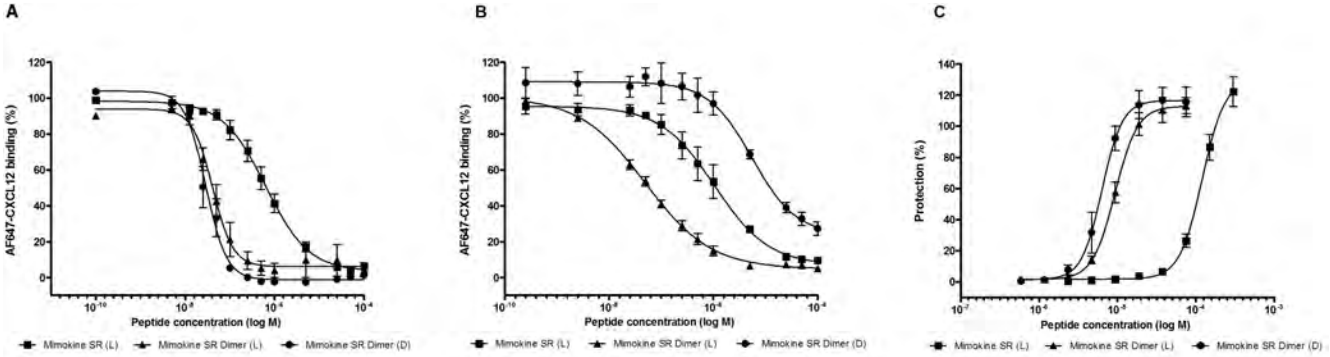
213 Optimization of vCCL2-Based CXCR4 Inhibitors by Phage Display and Rational Design

Virginie Fievez[1]; Martyna Szpakowska[1]; Karthik Arumugam[1]; Amor Mosbah[2]; Sabrina Deroo[1]; Xavier Dervillez[1]; Pierre-Arnaud Gauthier[1]; Michele Baudy-Floc'h[2]; Carole Devaux[1]; Andy Chevigné[1]
[1]CRP-sante, Laboratory of Retrovirology, 84 Rue Val Fleuri, 1526 Luxembourg, Luxembourg; [2]Université de Rennes 1, UMR CNRS 6226, Avenue du Général Leclerc, 35042 Rennes, France

Background: The viral broad spectrum chemokine vCCL2/vMIP-II binds to CXCR4 and CXCR7 and protects host cells against HIV-1 infection. Peptide derived from vCCL2 N-terminus ($vCCL2_{1-21}$) displays modest CXCR4 binding affinity and antiviral properties compared to the parental chemokine but mutations within its CC motif have been shown to enhance its antiviral properties. In this study, we selected new vCCL2 derived peptides by means of phage display and further optimized them by rational design

Methods: A $vCCL2_{1-21}$ phage library in which cysteine at positions 11 and 12 ($C_{11}C_{12}$) (Mimokine) were fully randomized was first engineered and screened against CXCR4-proteoliposomes. The most potent selected Mimokines were then further optimized by D-amino acid replacement and dimerization. Finally, a set of L- and D-bivalent ligands were evaluated for their CXCR4/CXCR7 binding and antiviral properties

Results: Selection of $vCCL2_{1-21}$ library on CXCR4 resulted in the isolation of 4 Mimokines bearing FR, SR, VR and WL residues at positions C_{11} and C_{12}. These Mimokines fully protected MT-4 cells against infection by a HIV-1 X4 virus (HXB2) (IC_{50} = 60 to 185 μM) and exhibited 3 to 4-fold higher affinity for CXCR4 (IC_{50} = 480 to 740 nM) than the reference Mimokine SS (IC_{50} = 2164 nM). Molecular modelling and docking into CXCR4 3D structure suggested that the enhanced affinity of Mimokines FR, SR and VR for CXCR4 might be due to the formation of an additional salt bridge between the Mimokine Arg12 and the receptor sulfated Tyr21. The potency of the selected Mimokines was further enhanced by combining dimerization and D-amino acid substitution. Bivalent Mimokines SR, VR, FR and WL in D format exhibited 10 to 20-fold increase in CXCR4 binding affinity (IC_{50} = 29 to 44 nM) and 20 to 100-fold increase in antiviral activities (IC_{50} = 1,8 to 6.3 μM) when compared to their respective monomeric L-counterparts. Interestingly, these bivalent D-Mimokines displayed a 100-fold reduction in binding CXCR7 (IC_{50} = 5630 nM) when compared to the bivalent L-Mimokines, demonstrating that D-amino acid replacement improved both affinity and selectivity for CXCR4



Binding and antiviral properties of monomeric and dimeric Mimokine SR in format D and L. The binding of Mimokine SR analogs to CXCR4 (A) or CXCR7 (B) expressing cells was assessed in competition experiments using a fluorescently labelled CXCL12 (AF647-CXCL12). Protection of MT-4 cells conferred by a 3-fold serial dilutions of Mimokine SR analogs against the HIV-1 HXB2 virus (C).

Conclusions: Optimized bivalent D-Mimokines displayed 10 to 20-fold enhanced CXCR4 affinity and 20 to 100-fold improved antiviral properties when compared to the initial monomeric L-Mimokines. These bivalent D-Mimokines showed a reduced affinity for CXCR7 and may therefore serve as lead compounds for the further development of more selective CXCR4 HIV-1 inhibitors

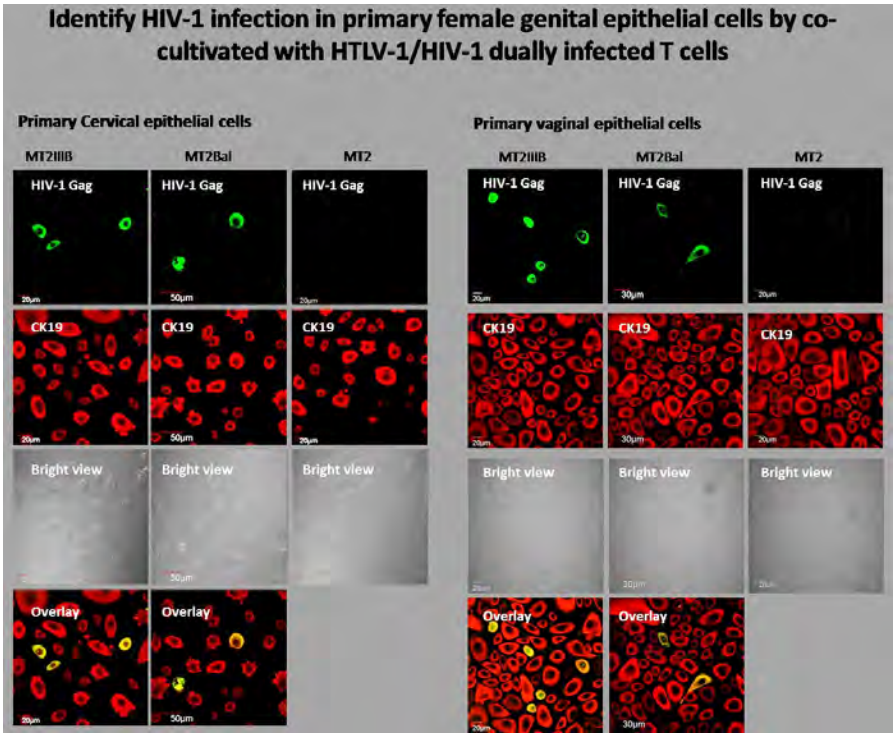
214 HIV-1 Infection of Female Primary Genital Epithelial Cells After Pseudotyping With HTLV-1: Potential Driver of Sexual Transmission of HIV-1

Yuyang Tang[1]; Alvin George[1]; Oksana Petrechko[1]; Brian Imbiakha[1]; Stephanie Sweet[1]; Yuetsu Tanaka[2]; Franklin Nouvet[1]; James E. Hildreth[1]
[1]University of California Davis, Davis, CA, US; [2]University of the Ryukyus, Nishihara-cho, Japan

Background: Young females are at high risk of HIV infection and constitute 75% of infected individuals in some sub-Saharan Africa countries. Some regions with high prevalence of HIV-1 are often also highly endemic for HTLV. HIV/HTLV co-infection in Africa, Latin America and the Caribbean basin is increasing and has emerged as a global health problem. In our recently published study we demonstrated that HIV-1 is able to acquire envelope glycoproteins of a gammaretrovirus during co-infection, in a process we called "natural pseudotyping", and expand its cellular tropism enabling it to infect primary female genital epithelial cells. Natural pseudotyping may dramatically increase risk of female HIV-1 infection during sexual intercourse and therefore could be a biological factor contributing to the devastating spread of HIV in young females in Africa and other regions of the world.

Methods: T cells were coinfected with both HIV-1 and HTLV-1. The progeny virus was exposed to primary vaginal and cervical epithelial cells. HIV-1 and HTLV-1 infection was measured by immunofluorescence staining with antibody anti-HIV-1 Gag antibody or anti-HTLV-1 Gag, the viral release from epithelial cells was measured by ELISA and qRT-PCR.

Results: Progeny virus from HTLV-1/HIV-1 co-infected T cells was capable of infecting primary vaginal and cervical epithelial cells via both cell-associated and free virus mediated infection. No HIV-1 infection was observed from epithelial cells exposed to progeny virus from T cells infected with HIV-1 alone. Infection of primary genital cells was significantly reduced by antisera against the HTLV-1 glycoprotein, indicating that HIV-1 infection was mediated by the HTLV glycoprotein. Active HIV-1 replication infection in primary genital epithelial cells was confirmed by inhibition with protease inhibitors. However, HIV-1 reverse transcriptase inhibitors AZT or Rilpivirine only partially blocked HIV-1 infection in primary genital epithelial cells. Further analysis indicated that AZT or Rilpivirine treatment blocked HIV-1 infection in cells infected with HIV-1 alone but not in cells infected by both HIV-1 and HTLV-1. Since AZT and Rilpivirine have very limited effects on HTLV-1 replication we conclude that HTLV-1 RT conferred resistance by HIV-1 to HIV-1 RT inhibitors.



Conclusions: Co-infection with HIV-1 and HTLV-1 produces naturally pseudotyped HIV-1 capable of directly infecting primary female lower genital epithelial cells and that the pseudotyped HIV-1 may be resistant to RT inhibitors.

WEDNESDAY, FEBRUARY 25, 2015

Session P-A5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Envelopes, Receptors, and Tropism

215 Evaluation of HIV-1 Clones for Unique Properties Associated With Transmission

Katja Klein[1]; Annette Ratcliff[2]; Gabrielle Nickel[2]; Immaculate Nankya[2]; Mike Lobritz[2]; Yong Gao[2]; Robin Shattock[3]; Eric J. Arts[1]

[1]*University of Western Ontario, London, Canada;* [2]*Case Western Reserve University, Cleveland, OH, US;* [3]*Imperial College London, London, United Kingdom*

Background: In the vast majority of cases, mucosal HIV-1 infection is initiated by a single infectious virus or a small number of HIV-1 virions. Next to CCR5 receptor usage and envelope glycosylation, little is known about the phenotypic properties of these transmitted HIV-1 virions and the influence that phenotype plays in the genetic bottleneck selection process. We evaluated a number of acute/early and chronic HIV-1 viruses, isolated from the female genital tract and blood, in a series of genotypic and phenotypic assays to determine differences that may influence transmission fitness.

Methods: We analyzed the genetic diversity by next generation sequencing of acute/early HIV-1 isolated from the female genital tract and compared it to the diversity of HIV-1 in blood of the same patients. We then engineered chimeric viruses from acute and chronic envelope genes and evaluated them for host cell entry efficiency and kinetics, receptor affinity, replication fitness, sensitivity to entry inhibitors and transmission using *ex vivo* human mucosal explant tissue.

Results: Genetic analysis revealed that acute/early HIV-1 isolates from blood are homogeneous while HIV-1 in the female genital tract showed high diversity. Furthermore acute isolates from the female genital tract displayed higher envelope glycosylation compared to HIV-1 from blood. We observed that both, acute and chronic HIV-1 isolates had similar entry kinetics, sensitivity to entry inhibitors and replicative fitness in primary cells. In contrast the evaluation of acute and chronic HIV-1 in human cervical and penile tissue clearly demonstrated that acute virions penetrate tissue, bind to residing DCs and establish infection of T cells more efficiently than chronic HIV-1, which were trapped and replicated in tissue. Higher transmission fitness of acute HIV correlated with reduced envelope N-linked glycosylation resulting in reduced lectin binding affinity.

Conclusions: Mucosal tissues, the major sites of heterosexual HIV transmission have high levels of extracellular soluble lectins and C-type lectins expressed on epithelial cells which are designed to prevent infection of high mannose-containing pathogens. As such, HIV-1 with reduced N-linked glycans may be passively selected for transmission by escaping the "lectin-trap".

216 Selection of HIV Env Mutants With Altered Trimers by EMPIRIC Saturation Mutagenesis

Maria Duenas-Decamp; Li Jiang; Dan Bolon; Paul R. Clapham

University of Massachusetts Medical School, Worcester, MA, US

Background: HIV-1 vaccines need to elicit neutralizing antibodies (nabs) that target conserved Env epitopes to protect against diverse HIV-1. To achieve this, we need to increase our knowledge on how different amino acids affect Env trimer structure. Native Env trimers are likely to be closed to protect against nabs and only triggered to open by CD4. Our hypothesis is that tightly closed trimers will (1) hide immunodominant non-neutralizing or strain specific Env sites e.g. V3 loop, and (2) expose conserved epitopes e.g. on the trimer association domain. To identify Env residues that maintain a closed trimer, we used EMPIRIC (Exceedingly Meticulous and Parallel Investigation of Randomized Individual

Codons) saturation mutagenesis. We created a library of viruses carrying every possible amino acid in an Env region downstream from the CD4 binding loop. Following fitness competition in PBMCs in the absence of immune pressure, we identified several mutations that facilitate trimer opening.

Methods: We used EMPIRIC saturation mutagenesis to create a plasmid library containing all possible mutations for aa 371-380 of LN40 Env in NL4-3 full length virus. We recovered viruses from transfected 293T cells and then infected PBMCs. To quantify competitive fitness, we measured the abundance of each mutant before and after PBMC infection using deep sequencing. We then studied 14 mutations that were selected at wt levels or higher in PBMCs. We evaluated changes in Env structure by testing the sensitivity of Env+ pseudovirions to neutralization by sCD4 and mabs b6, b12, 447-52D and 2G12.

Results: Substitutions at aa380 conferred sensitivity to CD4bs mab, b6 and V3 mab, 447-52D, which recognize more open trimers e.g. on laboratory strains. Substitutions at aa373, 375 in addition to 380 increased sensitivity to sCD4 compared to wt. Several substitutions conferred increased sensitivity to the CD4bs mab b12, with changes in residues 373 and 375 affecting b12, sCD4, 447-52D and 2G12 sensitivity together. Our data indicate that the residues identified play an important role in enhancing CD4 binding and/or regulating trimer opening.

Conclusions: We identified specific amino acids in a region of Env proximal to the CD4 binding loop that facilitate trimer opening, increasing the exposure of neutralizing epitopes and sensitivity to sCD4. The identification of specific positions in gp120 that affect trimer opening will help the design of stably closed trimers for use in vaccines.

217 Characterization of HIV-1 Envelopes in Acutely and Chronically Infected Injection Drug Users

Behzad Etemad[1]; Oscar A. Gonzalez[1]; Laura F. White[2]; Oliver B. Laeyendecker[3]; Greg D. Kirk[3]; Shruti Mehta[3]; **Manish Sagar**[1]

[1]Boston University School of Medicine, Boston, MA, US; [2]Boston University, Boston, MA, US; [3]Johns Hopkins University, Baltimore, MD, US

Background: Mucosally acquired HIV-1 infection results from a limited number of variants, and these infecting strains potentially have unique properties, such as increased susceptibility to entry blockers, relative interferon-alpha (IFN-α) resistance, and replication differences in some primary cells. There is no data about the phenotypic properties of HIV-1 envelope variants found early after acquisition among subjects infected through injection drug use (IDU).

Methods: We compared the characteristics of virus envelopes among injection drug users sampled prior to seroconversion (HIV RNA+/Ab-), within 1 year (early), and more than 2 years (chronic) after estimated acquisition. Full-length HIV-1 envelopes generated from pooling multiple bulk PCRs were incorporated into a HIV-1 NL4-3 backbone to create replication competent recombinant viruses. The envelopes were examined for various phenotypes, such as replication kinetics in primary cells, gut homing receptor, $\alpha4\beta7$, reactivity, and sensitivity to IFN-α. Summary phenotypic characteristics were compared using the Wilcoxon rank-sum test.

Results: Virus envelopes from 7 HIV RNA+/Ab- subjects possessed lower genetic diversity ($p = 0.05$) and divergence ($p = 0.05$) compared to 7 unrelated individuals sampled during the chronic phase of disease. The HIV RNA+/Ab- as compared to the chronic phase envelopes were significantly more sensitive to a CCR5 receptor inhibitor ($p = 0.03$) and IFN-α ($p = 0.008$) and showed a statistical trend toward greater sensitivity to a fusion blocker ($p = 0.07$). The early as compared to chronic infection envelopes also demonstrated a statistical trend or significantly greater sensitivity to CCR5 ($p = 0.06$) and fusion inhibitor ($p = 0.01$) and IFN- α ($p = 0.1$). The HIV RNA+/Ab- as compared to chronic envelope viruses replicated to a lower extent in mature monocyte derived dendritic cells – CD4+ T cell co-cultures ($p = 0.03$), but there were no significant replication differences in other primary cells, including those expressing high levels of the $\alpha4\beta7$ integrin, among the viruses with envelopes from the 3 different stages of infection.

Conclusions: Similar to mucosal acquisition, HIV-1 envelope quasispecies present in injection drug users prior to seroconversion have unique phenotypic properties compared to those circulating during the chronic phase of disease. This suggests that there is selection for specific HIV-1 variants during injection drug use.

218 Phenotypic Characterization of Transmitted/Founder Virus in HIV-1 Transmission Pairs

Corinna S. Oberle[1]; Beda Joos[1]; Nottania K. Campbell[1]; David Beauparlant[1]; Herbert Kuster[1]; Corinne Schenkel[1]; Peter Rusert[1]; Alexandra Trkola[1]; Karin J. Metzner[1]; Huldrych F. Günthard[1]

[1]University Hospital Zurich, Zurich, Switzerland; [2]Institute of Medical Virology, Zurich, Switzerland

Background: In 60-90% of mucosal HIV-1 transmissions a single transmitted/founder (T/F) virus from a genetically diverse virus population of the transmitter infects the recipient. Whether HIV-1 transmission is a stochastic process or the T/F viruses have beneficial features facilitating transmission and infection is controversially discussed. Here, we investigated the phenotypes of viruses isolated from transmission pairs in order to discover properties that might favor transmission.

Methods: Based on phylogenetic analyses of HIV-1 *polymerase* and *envelope* sequences and clinical data from patients enrolled in the Zurich Primary HIV-1 Infection Study (ZPHI) and Swiss HIV Cohort Study (SHCS), 9 potential transmission pairs of subtype B were identified and primary virus isolates of transmitter and recipient (acutely infected patients with single T/F virus) at the nearest time point of transmission were generated. Virus isolates were characterized in respect to replication capacity in peripheral blood mononuclear cells (PBMCs) in the absence and presence of IFN-α and in monocyte-derived macrophages (MDMs). Furthermore, sensitivity to different entry inhibitors (Maraviroc, DARPin 57.2, soluble CD4, T-20) and neutralizing antibodies (2G12, 4E10, 2F5), and the entry kinetics of these virus isolates were studied.

Results: All virus isolates replicated efficiently in PBMCs and 15 of 18 virus isolates were capable to replicate in MDMs, however, to a lesser extent. No clear pattern could be observed: In some transmission pairs, the virus isolate from the transmitter replicated more efficiently in MDMs and/or PBMCs and vice versa in other pairs. All virus isolates were sensitive to IFN-α; yet the degree to which replication was reduced varied within and between transmission pairs. In terms of entry, virus isolates from the same transmission pair were inhibited to similar degrees by different entry inhibitors and neutralizing antibodies. Moreover, virus obtained from transmitter and recipient showed similar entry kinetics.

Conclusions: For some transmission pairs, differences in replication capacities in both PBMCs in the absence or presence of IFN-α and MDMs were detected, yet we could not identify a common property shared by T/F viruses. T/F viruses and the virus population of the transmitter showed similar sensitivity to entry inhibitors/neutralizing antibodies and similar entry kinetics. Hence, according to the investigated parameters no signifying phenotypic pattern could be attributed to T/F viruses.

219 HIV Coreceptor Tropism Switching Is Correlated With Binding Affinity to CXCR4

Homero Vazquez[1]; Antoine Chaillon[2]; Douglas D. Richman[3]; Sara Gianella Weibel[1]; Gabriel Wagner[1]; David M. Smith[3]

[1]University of California San Diego, San Diego, CA, US; [2]Inserm UMR U966, Tours, France; [3]Veterans Affairs Medical Center, San Diego, CA, US

Background: The switch of HIV-1 co-receptor tropism from CCR5 (R5) to CXCR4 (X4) during the course of infection is associated with changes in the V3 region; however, little is known about the structural binding between V3 and R5 and X4 co-receptors during tropism switching. We used an *in-silico* approach to model the physical properties of the gp120-CD4-R5/X4 complexes during these changes.

Methods: A molecular dynamics (MD) and continuum-electrostatics poison-Boltzmann approach was used for generation of interaction models and calculation of binding affinity (BA). Since no experimentally derived structure is available, we first mapped well-characterized R5 and X4 strains onto the backbone of V3, followed by molecular dynamic simulations and docking of simulated structures into R5 and X4 to generate a gp120-CD4-R5/X4 complex interaction model. A database of viral sequences (n= 42 sequences, 38 from macaques, and 4 from patients) that switched over time from R5 to X4 tropism was then utilized to investigate changes in BA during tropism switching. All sequences were modeled onto the backbone structures of the interaction models of both R5 and X4; and BA amongst gp120, CD4, and R5/X4 was also calculated.

Results: When comparing the gp120-CD4-R5 complex in R5 tropic virus to the gp120-CD4-X4 complex in X4 tropic virus, the higher charge on the V3 associated with X4 tropism led to greater thermodynamic stability via favorable electrostatic interactions in the gp120-CD4-X4 complex than V3 that was tropic to R5. Cross-sectional analysis of X4 tropic versus R5 tropic sequences identified a significant correlation between the BA of gp120 to CD4+X4 ($p<0.001$) but not between the BA of gp120 to CD4+R5 ($p=0.35$). In longitudinal analysis, switching tropism from R5 to X4 was associated with a significant decline in BA between gp120 to CD4+R5 by 52%-76% and a concomitant increase in BA between gp120 to CD4+X4 by 0.4%-29.3%.

Conclusions: Structural modeling demonstrated that X4 tropism is highly associated with the BA of gp120 to CD4+X4, while R5 tropism is not associated with the BA between gp120 and CD4+R5. Further, when a viral population switches from R5 to X4 tropism, the thermodynamic stability of the gp120-CD4-X4 complex considerably increases while the thermodynamic stability of the gp120-CD4-R5 complex decreases. Together, these data provide new insights into the mechanisms of viral co-receptor interaction and co-receptor tropism switching.

220 Selective Cell-Free or Cell-to-Cell HIV-1 Infection by gp41 Cytoplasmic Tail Mutants

Natasha D. Durham[1]; Benjamin K. Chen[1]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, US; [2]Icahn School of Medicine at Mount Sinai, New York, NY, US

Background: The gp41 transmembrane subunit of the HIV-1 envelope (Env) has a cytoplasmic tail (CT) ~150 amino acids (aa) long. The CT has several functions during the viral life cycle, including the i) endocytosis of cell-surface Env ii) packaging Env into viral particles and iii) controlling the fusogenic potential of Env. Full truncation of the gp41 CT (ΔCT144) does not directly impair viral fusion and can generate infectious virus in a cell-type dependent manner. Smaller deletions result in non-infectious virus particles, although Env is still expressed and packaged. Only the full truncation, ΔCT144, has been tested in the context of cell-to-cell infection. We therefore set out to systematically examine which domains of the CT are required for cell-to-cell infectivity in comparison to those needed for cell-free infection.

Methods: We constructed a series of truncation mutants that remove three major structural motifs in the gp41 CT, LLP-1, LLP-3 and LLP-2. Mutants were examined for HIV-1 envelope expression levels on the surface of transfected T-cells and total Env levels packaged onto virus particles. We used flow-cytometry to assess the single-round infectivity of cell-free and cell-associated virus in MT4 and primary CD4+ T-cells.

Results: Small truncations ≤43 aa that remove LLP-1 severely impaired the infectivity of cell-free virus, while cell-to-cell infection remained ~50% as infectious as WT HIV-1. Similar selective deficiency in cell-free but not cell-to-cell infection was observed with the LLP-3 point mutants. Conversely, large truncations ≥93 aa severely impaired cell-to-cell infectivity while maintaining infectious viral particles. Intermediate truncations (59-90 aa) showed profound impairment of both modes of infection.

Conclusions: We identified gp41 CT mutants with striking selective deficiencies in cell-free but not cell-to-cell infectivity, or vice versa. Our results indicate that functional properties of Env required for cell-free and cell-to-cell infection are genetically distinct. These differences may reflect a different intrinsic regulatory influence of the CT on cell-associated versus particle-associated Env, or differential interaction with host or viral proteins. Our findings highlight the positive and negative potential of the gp41 CT in regulating cell-free and cell-to-cell HIV-1 infection. We will use these mutants in future studies to define the contributions of cell-free and cell-to-cell infection *in vivo*, and to study one mode of infection in isolation.

221 Analysis of Viral Evolution in the Blood Reveals Potential Insight Into the Evolution of Macrophage Tropism

Maria M. Bednar[1]; LiHua Ping[1]; Kathryn Arrildt[1]; Christa Sturdevant[2]; Sarah B. Joseph[1]; Laura Kincer[1]; Celia LaBranche[2]; David Montefiori[2]; Myron Cohen[3]; Ronald Swanstrom[1]

[1]University of North Carolina, Durham, NC, US; [2]Duke University, Durham, NC, US; [3]University of North Carolina, Chapel Hill, NC, US

Background: Understanding the evolution of entry phenotype of HIV-1 is essential for our understanding of HIV-1 pathogenesis, latency, and disease progression**.** The use of a more precise assay to define entry phenotype based on the ability of HIV-1 to use low levels of CD4 for efficient entry has clarified the relationship of viruses that have evolved to infect macrophages as distinct from R5 viruses that predominantly replicate in T cells. We have used this assay to identify infrequent examples of macrophage-tropic (M-tropic) viruses and partially M-tropic viruses (intermediate) in cerebral spinal fluid and genital tract. However the prevalence of M-tropic viruses in other compartments, such as the blood, remains unknown. We set out to determine if M-tropic viruses ever reach a point of systemic infection.

Methods: Viral RNA was isolated from blood plasma samples from viremic subjects infected with either subtype B or subtype C HIV-1, and with CD4+ T cell counts of <100 cell/mm^3. Individual *env* gene were isolated, cloned and analyzed for receptor usage using Affinofile cells, in order to determine the viral entry phenotype. Susceptibility of pseudoviruses to soluble CD4 was also evaluated.

Results: 18 subtype B and 20 subtype C late-stage infected subjects were examined. As expected for late stage subjects, we identified X4 lineages in over 50% of the subjects. To date, no examples of efficient use of low CD4 for entry (M-tropic virus) have been found in the blood. However, we do occasionally see a level of infection on CD4-low cells that is marginally greater than that of the typical R5 T cell-tropic virus. This intermediate phenotype has also been seen in the CSF and genital tract. This new group of viruses showed increased sensitivity to soluble CD4 that is comparable to macrophage-tropic viruses.

Conclusions: Using the definition of M-tropic virus as the ability to utilize low levels of CD4, leads to the conclusion that these variants are rare and are potentially limited to specific compartments of the body. The appearance of intermediate phenotypes in the blood argues that there may be some evolution toward macrophage tropism taking place in compartments that shed virus into the blood late in disease. The high level of sensitivity to soluble CD4 among intermediate viruses suggests that the evolution to M-tropism is at least a two-step process where the viruses first become more sensitive to interaction with CD4 followed by more efficient fusion.

222 Mechanistic Differences in Interactions of HIV-1 and HIV-2 With Dendritic Cells

Suzanne D. Kijewski; Hisashi Akiyama; Caitlin Miller; Nora P. Ramirez; Rahm Gummuluru

Boston University School of Medicine, Boston, MA, US

Background: HIV-2 infection has been restricted predominantly to West Africa; in contrast HIV-1 has spread rapidly and accounts for 95% of all HIV infections globally. Interestingly, HIV-2 infected individuals maintain low viral loads and have lower mortality rates than HIV-1 infected individuals. The mechanistic basis for viral control and slower progression to AIDS in HIV-2 infected individuals remains unclear. We hypothesized that reduced interaction of HIV-2 with CD169, the primary HIV-1 attachment factor on myeloid dendritic cells (DCs) that targets captured virus particles to the trans infection pathway, plays an important role in its restricted pathogenesis.

Methods: We constructed an HIV-2 proviral plasmid that encodes GFP between MA and CA and flanked by protease cleavage sites (HIV-2-iGFP), such that infectious virions contain GFP, similar to the previously described HIV-1-iGFP proviral clone (*J. Virol. 2007, 81:12596*). To examine interactions of HIV-2 with CD169, THP1 cells constitutively expressing CD169 (THP1/CD169) were pulsed with HIV-1iGFP or HIV-2iGFP virions and virus capture in the presence or absence of αCD169 blocking antibodies was determined by flow cytometry. Intra-cellular localization of HIV-1-iGFP or HIV-2-iGFP within mature DCs was determined by immunofluorescence microscopy. To determine access of HIV-2 to the CD169 mediated trans infection pathway, mature DCs were exposed to GFP-expressing single-cycle of replication competent HIV-2 virus pseudotyped with HIV-2 Env, and then co-cultured with autologous CD4$^+$ T cells.

Results: We have previously shown that HIV-1 evades cell-intrinsic restrictions in DCs by exploiting CD169 for enhanced transfer to $CD4^+$ T lymphocytes. Interestingly, there was a 3-fold reduction in capture of HIV-2 compared to HIV-1 by THP1/CD169 cells. Similar reduction in CD169 specific capture is seen with mature DCs, though both HIV-1 and HIV-2 virions were localized following capture within a $CD81^+$ compartment. Though HIV-1 and HIV-2 are equally infectious for $CD4^+$ T cells, there was a 7-fold decrease in mature DC-mediated HIV-2 trans infection of $CD4^+$ T cells compared to HIV-1 suggesting that HIV-2 might interact with additional receptors on the mature DC surface, which inhibit access to the trans-infection pathway.

Conclusions: We conclude that a reduced interaction of HIV-2 with CD169 inhibits access of HIV-2 to the DC-mediated trans infection pathway and might result in attenuated dissemination in vivo.

223 Identification of the First Nonhuman Primate CD4 Receptor for T/F HIV-1 Isolates

Nicholas Meyerson[2]; **Amit Sharma**[1]; Gregory Wilkerson[3]; Julie M. Overbaugh[1]; Sara Sawyer[2]

[1]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [2]The University of Texas at Austin, Austin, TX, US; [3]University of Texas, MD Anderson Cancer Center, Bastrop, TX, US

Background: Nonhuman primate species are resistant to HIV-1 infection, in most cases due to the inability of their CD4 to function as HIV-1 receptor for viral entry and/or species-specific host factors that restrict HIV-1 replication. Envelopes (Envs) from lab-adapted and some chronic-stage isolates of HIV-1 use the CD4 receptor encoded by multiple primate species, including macaque CD4. However, only the human CD4 receptor can mediate entry of Envs from HIV-1 variants representing transmitted/founder (T/F) viruses, which are most relevant to the HIV-1 pandemic. CCR5 presents an additional barrier to entry in many other primate species. These factors have limited the development of animal models to study viral pathogenesis of these more clinically relevant, T/F HIV-1 strains.

Methods: In this study we analyzed the CD4 sequence of multiple individuals from 11 different nonhuman primate species, including two Old World macaque species and five different species of New World monkeys. We also utilized human SNP databases and previous reports on *CD4* diversity in chimpanzees and three different species of Old World monkeys. We cloned selected *CD4* and *CCR5* alleles from primate species that were polymorphic at sites identified in previous studies as critical for HIV-1 envelope binding and/or entry. We tested these *CD4* and *CCR5* alleles for their ability to function as HIV-1 receptor and coreceptor, respectively, by generating cells expressing different combinations of these receptors.

Results: Multiple *CD4* alleles were identified in one New World monkey species, the Spix's owl monkey (*Aotus vociferans*), which encode CD4s that support entry mediated by circulating Envs from all of the major clades of HIV-1 group M. The Spix's Owl monkey CD4 receptor facilitated entry at levels similar to the human receptor in combination with human CCR5 and pig-tailed macaque CCR5. Interestingly, CCR5 from Spix's owl monkey was not a functional coreceptor when combined with their permissible CD4.

Conclusions: We demonstrate that CD4 is polymorphic in primate species at sites critical for HIV-1 entry. We have identified the first nonhuman primate CD4 compatible with entry of transmitted, circulating HIV-1 Envs. These findings support efforts to use novel strategies, including genetic screening, for developing better HIV-1 animal models.

224LB Vpr Increases Env Spikes on Virions to Enhance HIV-1 Replication in Nondividing Myeloid Cells

Tao Zhou[1]; Xianfeng Zhang[2]; **Yonghui Zheng**[1]

[1]Michigan State University, East Lansing, MI, US; [2]Harbin Veterinary Research Institute, Harbin, China

Background: Vpr plays an important role in maintenance of high viral load and disease progression *in vivo* through unknown mechanisms. Vpr has a very important function *in vitro*, enhancing viral replication in non-dividing myeloid cells, but the mechanism is likewise unknown. Because these cells are primary targets for HIV-1 infection and contribute to viral persistence, understanding how Vpr enhances HIV-1 replication *in vitro* is critically important to understanding the functional role of Vpr *in vivo*. Notably, Vpr is packaged into HIV-1 particles at large numbers via a specific interaction with Gag, and Vpr activates the oxidative stress pathway in mammalian cells and fission yeast. However, it is still unknown how these Vpr activities contribute to the enhancement of viral replication.

Methods: Previously, we identified a human T cell line CEM.NKR (NKR), where we reported that Vpr is absolutely required for HIV-1 replication. We also reported that Env is misfolded and rapidly degraded via the ER-associated protein degradation (ERAD) pathway in these cells. We then investigated HIV-1 replication, Env expression, and Env incorporation in NKR cells, monocyte-derived macrophages (MDM), and monocyte-derived dendritic cells, after creating a panel of Vpr mutations in HIV-1 proviral constructs. We also compared how Env was degraded in the presence or absence of Vpr by activating the oxidative stress pathway and/or inhibiting the ERAD pathway.

Results: It was found that when Vpr was not expressed, Env was more aggressively degraded via the ERAD pathway. Vpr could strongly block this degradation, resulting in significant increase of Env expression. A single A30L mutation within the 1st α-helix of Vpr could disrupt this activity, suggesting that the N-terminal region of Vpr plays a critical role in Env expression. Interestingly, although Env could be expressed, it was not efficiently incorporated into virions unless Vpr was expressed. However, Vpr was not required for Env trafficking to the cell surface. Using Vpr packaging deficient mutants, it was further uncovered that the Env incorporation was dependent on the Vpr incorporation. Importantly, Vpr was found to interact with both Gag and Env, resulting in increase of Env incorporation.

Conclusions: We concluded that Vpr increases Env expression likely by promoting Env folding via the oxidative stress pathway, and it also increases Env incorporation via bridging Env with Gag, resulting in increase of Env spikes on virions and enhancement of HIV-1 replication.

THURSDAY, FEBRUARY 26, 2015

Session P-A6 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Nef Functions

225 Env and Nef Cooperatively Contribute to HIV-1–Induced pDC Activation via CD4-Dependent Mechanisms

Natalia J. Reszka-Blanco[1]; Vijay Sivaraman[1]; Liguo Zhang[2]; Lishan Su[1]

[1]University of North Carolina, Chapel Hill, NC, US; [2]Key Lab of Infection and Immunity, Insitute of Biophysics, Chinese Academy of Science, Beijing, China

Background: HIV-1 infection induces high levels of type I IFN (IFN-I). The function of IFN-I in HIV-1 infection is not entirely defined, with results showing either its beneficial effect in anti-vial therapy or contribution to the HIV-1 related immune activation and CD4 T cell loss. Moreover, HIV-1 early isolates are resistant to IFN-I control and can succeed in establishing systemic infection despite the high level of IFN-I. Plasmacytoid dendritic cells (pDC) are the major source of IFN-I and play a critical role in the response to HIV-1. pDC are rapidly activated by HIV-1 infection and are implicated in both early reduction of viral load and HIV-1 induced pathogenesis. Interestingly cell-free virions of most HIV-1 isolates

are relatively weak stimulants of pDC and the mechanism of HIV-1 recognition by pDC and pDC activation is not clearly defined. Using two HIV-1 isolates, designated R3A and R3B, we aimed to determine the critical elements of the HIV-1 viral particle required for IFN-I induction in pDC.

Methods: Human PBMC and pDC were used to study the IFNa induction. IFNa was measured by Elisa. Viral production was quantified by p24-Elisa. Ala-substitution mutagenesis was used to analyze the Nef-functional domains.

Results: In this study we showed that two highly similar HIV-1 variants isolated from a rapid progressor had distinct activity to stimulate pDC and induce IFNa, which in turn correlated with their relative pathogenic activity. The highly pathogenic HIV-1 isolate R3A induced robust IFNa production in pDC, while R3B did not. The viral determinant of efficient IFNa induction was mapped to R3A Env and its V1V2 region with enhanced CD4 binding activity. Interestingly, the Nef gene in R3A was also required for the IFNa induction from pDC. To define which Nef domain or activity are required for increased IFNa induction, we analyzed a panel of R3A Nef functional mutants. We showed that Nef domains involved in CD4 downregulation are necessary for R3A to induce IFNa in pDC.

Conclusions: Our data indicate that HIV-1 induced pDC activations depends on (1) the efficacy of envelop to bind CD4 receptor and (2) the Nef activity involved in CD4 downregulation. Our work provides new insights into the mechanism by which HIV-1 stimulates IFNa in pDC and describes novel function of Nef protein which contributes to increased IFNa production and therefore to the pathogenesis of HIV-1 infection.

226 Naturally Occurring Polymorphisms in HIV-1 Nef Impair Its Functions and Decrease Viral Replication Capacity

Thomas Vollbrecht[2]; Lorelei Bornfleth[1]; Patricia Frohnen[1]; Martha J. Lewis[1]

[1]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US; [2]University of California San Diego (UCSD), La Jolla, CA, US

Background: The multifunctional accessory HIV-1 protein Nef plays a pivotal role in viral pathogenesis. Key functions of Nef include the downregulation of CD4 and MHC class-I molecules from the surface of HIV-1 infected cells. Previously, we have identified new polymorphisms in Nef from nine subjects under selection pressure by HIV specific CTL. Here we investigate the effect of these polymorphisms on the ability of Nef to downregulate CD4 and MHC class-I molecules, as well as the impact of these polymorphisms on viral replication capacity.

Methods: The polymorphisms N52A, N52S, A84D, Y135F, G140R, S169I, H171N, H171P, H71G, D175E, D175N, and V180E were created individually within the plasmid AA1305, a NL43-based proviral vector with the murine CD24 (HSA) reporter gene in vpr, to generate VSV-G pseudotyped replication defective reporter viruses. Additionally, we introduced these mutations into the plasmid p8310, a NL4-3 based half-genome plasmid to generate replication competent reporter viruses. CEMx174.T1 cells were transduced with the replication defective individual viruses to determine the downregulation of MHC class-I and CD4 by flow cytometry. Viral replication capacity was assessed using gDNA and qPCR from PBMC transduced with replication competent reporter viruses.

Results: We found in total seven polymorphisms (N52S, A84D, Y135F, G140R, S169I, H171N, H171P) resulting in a significant reduction of HLAA*02 downregulation and five polymorphisms (A84D, G140R, S169I, H171N, H171P) with a significant decrease in CD4 downregulation compared to wild type NL4-3 Nef. Nef with either of two polymorphisms, A84D and G140R was defective for downregulation of HLA-A*02 and CD4. Additionally, virus with the G140R polymorphism also exhibited a significantly decreased viral replication capacity.

Conclusions: Our study shows that the majority of the tested polymorphisms exert an inhibitory effect on Nef's functions. The two polymorphisms A84D and G140R block CD4 and MHC class-I downregulation by Nef. Additionally, the G140R polymorphism also results in a decreased viral replication capacity in primary cells. All tested variants were natural occurring polymorphisms that were previously identified in primary isolates.

Our findings lead the way for better Nef targeting by vaccines and for the development of highly effective Nef inhibitors. These results demonstrate new potential targets for immunization or pharmacological intervention strategies.

227 Dynamic Range of Down-Regulation of HIV-1 Entry Receptors by Primary Nef Isolates

Mako Toyoda[1]; Yoko Ogata[1]; Macdonald Mahiti[1]; Florencia Pereyra[3]; Toshiyuki Miura[2]; Bruce Walker[3]; Zabrina L. Brumme[4]; Mark A. Brockman[4]; Takamasa Ueno[1]

[1]Kumamoto University, Kumamoto, Japan; [2]University of Tokyo, Tokyo, Japan; [3]Ragon Institute of MGH, MIT and Harvard University, Cambridge, MA, US; [4]Simon Fraser University, Burnaby, Canada

Background: HIV-1 Nef down-regulates the viral entry receptor CD4 as well as the co-receptors CCR5 and CXCR4 from the surface of infected cells, leading to promotion of viral replication through super-infection resistance and other pathways. In vitro mutagenesis of laboratory strains have identified various sequence motifs within Nef that modulate these functions. However, it remains unclear whether primary Nef sequences isolated from patients with different disease status also modulate down-regulation of these receptors via these same sequence motifs.

Methods: Nef clones were amplified from plasma viral RNA of 45 elite controllers (EC) and 46 chronic progressors (CP) and cloned into an expression plasmid. Additional mutations and reversions were introduced into these primary Nef clones to identify functionally important residues and motifs. The resultant plasmids were transfected into TZM-bl cells and CEM cells. Steady-state Nef expression level and cell surface expression of viral receptors were analyzed by Western blot and flow cytometry, respectively.

Results: Nef clones from EC showed significantly impaired activity in down-regulation of CD4 and CCR5, compared to those from CP ($p<0.001$), whereas the difference in down-regulation activity of CXCR4 was not statistical significance ($p=0.05$). The ability to down-regulate CD4 and CCR5 correlated positively in both EC and CP ($R>0.7$, $p<0.001$), suggesting that both activities are simultaneously required in vivo. Nef codon-function analyses failed to identify residues significantly associated with Nef functions. Instead, mutagenesis studies on three EC Nef clones showing substantially diminished functions revealed that multiple residues were involved in altered Nef functions and protein expression level. Specifically, polymorphisms at the highly conserved tryptophan residues (e.g., Trp-57 and Trp-183) and within known CTL epitope regions were responsible for reduced Nef functions in these clones.

Conclusions: Reduced ability of Nef to down-regulate viral entry receptors appear to be mediated by multiple sequence motifs in primary Nef isolates, including those not identified in in vitro mutagenesis studies. Very rare polymorphisms as well as polymorphisms at immune-reactive sites were involved in this phenomenon in EC. Results suggest that functional attenuation of Nef in EC is mediated by complex polymorphism networks in individual Nef sequences.

228 Differential Down-Regulation of HLA Class I Allotypes by HIV-1 Nef Primary Isolates

Macdonald Mahiti[1]; Xiaofei Jia[2]; Mako Toyoda[1]; Francis Mwimanzi[1]; Bruce Walker[3]; Zabrina L. Brumme[4]; Mark Brockman[4]; Yong Xiong[2]; **Takamasa Ueno**[1]

[1]Kumamoto University, Kumamoto, Japan; [2]Yale University, New Haven, CT, US; [3]Ragon Institute of MGH, MIT and Harvard University, Boston, MA, US; [4]Simon Fraser University, Burnaby, Canada

Background: HIV-1 Nef, in conjunction with the host adaptor protein 1 (AP1), binds to the cytoplasmic region of HLA-A and HLA-B molecules and down-regulates them from the cell surface, thus allowing virus-infected cells to evade immune detection. Polymorphic residues within the HLA class I cytoplasmic region may affect Nef binding and subsequent down-regulation. However, the impact of HLA polymorphisms on recognition by primary Nef isolates, and the specific Nef regions responsible for flexible or differential down-regulation of various HLA-A and HLA-B molecules remain incompletely known.

Methods: 46 Nef clones isolated from chronically HIV subtype B-infected subjects were analyzed for down-regulation of HLA-A, HLA-B, and HLA-C on the surface of virus-infected cells by flow cytometry. A set of cells singly expressing various HLA class I alleles (HLA-A2, A24, A33, B35, B57, and Cw4) and a T cell line endogenously expressing multiple HLA class I, including HLA-A2 and HLA-B51, were analyzed.

Results: In 46 primary Nef clones, HLA-B showed greater resistance to Nef-mediated down-regulation compared to HLA-A ($p<0.001$), regardless of cell type examined. No Nef clone down-regulated HLA-C. A Nef codon-function analysis revealed that amino acid variations at Nef-202 substantially affected Nef-mediated HLA-A and HLA-B down-regulation function; this was subsequently confirmed by site-directed mutagenesis. Specifically, the Tyr-202 to Glu mutation alone was sufficient to selectively impair Nef-mediated HLA-B down-regulation. Moreover, a crystal structure of the ternary complex of Nef, HLA-A2 cytoplasmic tail peptide and the mu1 subunit of the host AP1 revealed that Nef-202 is in close proximity to the end of the HLA-A cytoplasmic tail where HLA-B lacks three amino acids compared to HLA-A, suggesting that this Nef residue may play a role in increased binding to the HLA-A cytoplasmic tail and facilitating down-regulation.

Conclusions: Taken together, results indicate that natural sequence variability within HIV-1 Nef affects the interaction with polymorphic HLA class I cytoplasmic tails for down-regulation, providing us with further insight into this complex pathway of immune evasion.

THURSDAY, FEBRUARY 26, 2015

Session P-B1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Viral Origins and Recombinant Forms

229 Geopolitical Effects in the Epidemiology of HIV-1 Subtype

Gkikas Magiorkinis[2]; Kostantinos Angelis[1]; Ioannis Mamais[1]; Angelos Hatzakis[1]; Jan Albert[3]; Glenn Lawyer[4]; Annemarie Wensing[5]; Charles Boucher[6]; Anne-Mieke Vandamme[7]; **Dimitrios Paraskevis**[1]

[1]University of Athens, Athens, Greece; [2]University of Oxford, Oxford, United Kingdom; [3]Karolinska Institutet, Stockholm, Sweden; [4]Max Planck Institute for Informatics, Saarbrücken, Germany; [5]University Medical Center Utrecht, Utrecht, Netherlands; [6]Erasmus University Medical Center, Rotterdam, Netherlands; [7]KU Leuven, Leuven, Belgium

Background: HIV-1 was discovered in the early 1980's when the virus had already established a pandemic. For at least three decades the epidemic in the Western World has been dominated by subtype B infections. Initially, the virus travelled from Africa through Haiti to the USA.

Methods: We assembled a globally representative dataset of HIV-1 subtype B sequences (N=8,370), by pooling molecular data collected from patient-cohorts and systematically selected molecular epidemiology studies from around the world. We analyzed the sequences using statistical phylogeography run on 250 bootstrap trees. To date, this is the largest global phylogeographic study of subtype B.

Results: We found that North America provided an active hub of dispersal for most local epidemics globally, while Western Europe also received infections from most of the other regions, namely from North and Central/South America, the Caribbean, Africa and Oceania. Significant migration events from Africa and Oceania to Europe, suggests that only a small number of subtype B infections are imported from these areas to Europe. Eastern Europe was initially isolated, but more recently provided spill-overs to Western Europe. Global phylogeographic trees show that European strains tend to cluster together, whereas North American strains are highly dispersed across the global genetic diversity. Sequences from North America also tend to have deeper roots than groups of sequences found in other regions, suggesting that North America has seeded the pandemic through multiple founder effect. Within Western Europe the United Kingdom was the most active in exchanging infections with non-European countries. As for mobility the most connected areas within Europe were found in the South. We also found that the degree of viral export from countries correlated with their number of subtype B infections. Major migrations can be connected to historical events.

Conclusions: The global spread of subtype B was not random. Viewing these patterns against the historical background, we observe that they strikingly mirror major geopolitical landmarks and trends since the end of World War II, namely the American influence over the Western World, the rise and fall of the Iron Curtain and major colonial relationships.

230 The 2 Phases of HIV-1 Group O Diversification

Marie Leoz[1]; Felix Feyertag[2]; Anfumbom Kfutwah[3]; Philippe Mauclere[4]; Guillaume Lachenal[5]; Florence Damond[6]; Veronique Lemee[1]; Francois Simon[7]; David Robertson[2]; Jean-Christophe Plantier[1]

[1]University Hospital Rouen, Rouen, France; [2]Manchester University, Manchester, United Kingdom; [3]Centre Pasteur du Cameroun, Yaounde, Cameroon; [4]Direction Interarmées du Service de Santé, Noumea, New Caledonia; [5]Université Paris Diderot, Paris, France; [6]APHP CHU Bichat Claude Bernard, Paris, France; [7]APHP CHU Saint Louis, Paris, France

Background: HIV-1 is subdivided into four groups: M, O, N and P. Group M is responsible for the pandemic, N and P are found in very few patients, and group O is endemic in Cameroon where it represents ~1% of HIV infections. Group O genetic diversity and evolution remain poorly characterised. Previous studies estimated its emergence to be as early as group M and have proposed different nomenclature systems. Here we fully investigate group O evolution, using an extensive dataset comprising sequences sampled from France, Cameroon and Gabon.

Methods: 190 HIV-O patients were sampled in France, Cameroon and Gabon between 1987 and 2012. Viral sequences from three regions of the genome were concatenated (total: 2012 base pairs) and analysed using phylogenetic and Bayesian population genetic methods to characterize evolutionary history.

Results: The tree topology was atypical, with a predominant clade emerging from a broad and genetically diverse base population. The presence of the Y181C mutation, naturally conferring resistance to non-nucleoside reverse transcriptase inhibitors, was significantly associated to the emergent clade.

The year of the most recent common ancestor (MRCA) was estimated to be around 1930, close to that of group M and consistent with previous estimates. Bayesian skyline analysis indicates group O diversification has gone through two exponential growth phases. The first phase, around 1950, resulted in widespread genetic diversity, while the second, from the late 1970s to the early 1990s, gave rise to the emergent clade.

According to the historical context in Cameroon, the first wave of group O expansion might have been favoured by iatrogenic routes of transmission between 1940 – 1960, while the second wave would rather be associated to the development of urbanization.

Conclusions: While groups O and M share a similar age, group O has remained largely confined to Cameroon. This has resulted in broad genetic diversity and intermixing of sub-populations, making it impossible to classify subtypes using a similar system as is used for group M. However, two subgroups can be observed corresponding to two successive phases of diversification. The viral properties of the two subgroups need to be investigated, to better understand why the now predominant clade was the most recent to emerge.

231 Evidence for More Major HIV-1M Lineages From the Early Stages of the HIV-1 Epidemic

Marcel Tongo Passo[1]; Wendy A. Burgers[2]; Eitel Mpoudi-Ngole[3]; Jeffrey Dorfman[1]; Darren P. Martin[4]

[1]International Center for Genetic Engineering and Biotechnology, Cape Town, Cape Town, South Africa; [2]Division of Medical Virology, University of Cape Town, Cape Town, South Africa; [3]Institute of Medical Research and Study of Medicinal Plants (IMPM), Yaoundé, Cameroon, Yaounde, Cameroon; [4]Computational Biology Group, University of Cape Town, Cape Town, South Africa

Background: One of the hallmarks of HIV-1 diversity is the occurrence of numerous mosaic circulating/unique recombinant forms (CRFs/URFs) which are not easily classifiable into any existing subtypes. There is, however, a lot of information stored within the genomes of these viruses which could be useful in efforts both to work out the early history of the HIV-1 pandemic, and to provide a better understanding on the origins and spread of different subtypes branching from near the roots of the HIV-1M phylogeny. Constantly improving phylogenetics-based analytical techniques and rapidly expanding HIV sequence datasets promise to yield important insights into how HIV first emerged.

Methods: In an effort to study the phylodynamics of the HIV-1M epidemic, we analysed a set of 577 genomic sequences including all published lineages from the Congo basin region and a selection of HIV lineages from the rest of the world designed to represent the full diversity of each subtype. A fully exploratory screen for recombination using RDP4 was performed with recombinant viruses being decomposed into their constituent parts. All sequences, including those belonging to "pure subtypes" were tested for recombination. Maximum likelihood phylogenetic analyses were used to identify rare parental sequences branching from near the root of the HIV-1M tree.

Results: Phylogenetic analyses of mostly recombination-free HIV-1M sequences indicated that many parental sequences of CRFs are not classifiable into the currently defined HIV-1M subtypes: Some of these parental lineages (including CRF02_AG, 04_cpx, 06_cpx and 11_cpx) contained more than 7000bp of unclassifiable sequence, suggesting that they are predominantly descended from what were/are major previously unidentified HIV-1M lineages that were likely epidemiologically relevant during the early stages of the HIV-1M epidemic. In addition, the phylogenetic tree also indicated that predominant parental sequences of some CRFs such as CRF47_BF and 05_DF were/are respectively highly divergent subgroup of B and D viruses. Furthermore, numerous sequences from the Congo basin branch basal to each subtype cluster, a finding consistent with this region being the geographic origin of the global HIV epidemic.

Conclusions: Our fully exploratory recombination screen suggests that many CRFs contain sequence fragments from previously unknown early diverging HIV-1 group M lineages. Such sequences could help tremendously with efforts to piece together the early evolutionary history of HIV-1M.

232 HIV-1/M+O Dual Infections and HIV-MO Recombinants in France From 2004 to 2014

Pierre Cappy[1]; Fabienne De Oliveira[1]; Veronique Lemee[1]; Jean-Louis Gaillard[2]; Laurence Bocquet[3]; Jean-Dominique Poveda[4]; Magali Bouvier[5]; Anne Maillard[6]; **Thomas Mourez**[1]; Jean-Christophe Plantier[1]

[1]Rouen University Hospital, Rouen, France; [2]Ambroise Paré Hospital, Paris, France; [3]Lille University Hospital, Lille, France; [4]CERBA Laboratory, Saint-Ouen L'Aumone, France; [5]Henri Mondor Hospital, Créteil, France; [6]Pontchaillou Hospital, Rennes, France

Background: Recombination is crucial for HIV evolution as pandemic HIV-M recombinants account for 20% of HIV-1 infections. HIV-M and -O co-circulation in Cameroon lead to dual infections and the subsequent generation of MO recombinants (MO). In France since 2004, one HIV-M/O superinfection, M+O dual infections and one MO have been described in patients linked to central Africa. In this study, we aimed to detect these forms in patients diagnosed in France with an HIV-O infection, and characterising the MO genomic patterns.

Methods: 141 samples from HIV-O infected patients were gathered from 2004 to 2014 by the French HIV-O Surveillance Network. M+O dual reactivities were screened for by gp120/V3 serotyping. On dually-reactive samples, group M and O specific PCRs were performed in *pol*, *acc* and *env* regions. Moreover, on HIV-O mono-reactive samples, M specific PCRs were also carried out when O amplification failed. Lastly, whole-genome sequencing was performed when possible, to characterise parental and recombinant strains.

Results: The presence of HIV-M and -O genomes was detected in 7% of patients (10/141). Two M+O dual infections were detected in 2 patients in 2004 and 2009. Two MO+O dual infections were detected on samples from 2005 and 2006 in epidemiologically linked patients and 1 MO+M+O triple infection in 2013. Finally 6 MO circulating alone were detected: 3 MO fully sequenced in 2008, 2010 and 2013 and 3 MO partially sequenced in 2010 (2 MO in one patient) and 2013. All the MO genetic patterns were different with breakpoints in the *acc* region (6/8), in LTRs (2/8) and $p17^{GAG}$ (1/8), *RT* (3/8), *INT* (2/8) and *gp41* (1/8) genes. The 2 viruses found in the same patient exhibited multiple breakpoints in *acc (2 and 5 respectively).*

Conclusions: Though all described in Cameroonian native patients, we showed HIV-M+O dual infections and MO recombinants circulate in France. Moreover, the presence of MO recombinants circulating alone and in epidemiologically linked patients demonstrate they are fit enough to be transmitted and spread. Finally, as HIV-O have still an impact on diagnosis and virological monitoring and are naturally resistant to non-nucleoside RT inhibitors, the transmission of HIV-M+O dual infections or MO recombinant forms carrying HIV-O genomic fragments underline the importance of searching for these forms, evaluate their spread dynamics and follow the possible emergence of a CRF_MO.

233 Evidence of Intra-Familial Transmission of an HIV-1 M/O Intergroup Recombinant Virus

Paul Alain T. Ngoupo[1]; Serge Alain Sadeuh-Mba[1]; Fabienne De Oliveira[2]; Valérie Ngono[1]; Laure Ngono[1]; Patrice Tchendjou[4]; Véronique Penlap Mbeng[3]; Richard Njouom[1]; Anfumbom Kfutwah[1]; Jean-Christophe Plantier[2]

[1]Centre Pasteur of Cameroon, Yaounde, Cameroon; [2]Virology, CHU Rouen, Rouen, France; [3]University of Yaounde I, Yaounde, Cameroon; [4]Epidemiology, Centre Pasteur of Cameroon, Yaounde, Cameroon

Background: HIV-1 groups M and O co-circulate in Cameroon and dual infections as well as HIV-1 M/O intergroup recombinant viruses have been reported in some patients. Recent data has described infection with HIV-1 M/O intergroup recombinant virus in the absence of dual infections thereby suggesting a direct transmission of the recombinant virus. In this study, we described and characterized an HIV-1 M/O intergroup recombinant virus in the absence of dual infection in a couple living in Cameroon. Here we provide for the first time evidence of a direct transmission of an HIV-1 M/O intergroup recombinant virus from one person to another.

Methods: Consecutive samples were obtained from a couple presenting for routine HIV viral load analysis. Prior to viral load analysis, each sample was subjected to HIV serotyping using envelope (V3 and gp41) peptides. These samples were subsequently screened for the presence of potential recombinant virus using specific PCRs targeting the Protease (PROT), Reverse transcriptase (RT), Integrase (INT) and envelope (gp41) genes of HIV-1 groups M and O. The previously reported recombination hotspot in the vpr gene was investigated using RT- nested PCRs. Near full length genome sequences of the viruses detected in both spouses were determined by amplification and sequencing of seven partially overlapping sub-genomic regions. Phylogenetic and similarity profile analyses were performed to investigate the genetic relatedness between viruses from both spouses.

Results: HIV serotyping indicated that samples from both patients (husband and wife) were reactive only with HIV-1 group O peptides thereby suggesting an infection with HIV-1 group O virus in both spouses. Molecular tests identified HIV-1 group M in the polymerase (PROT, RT and INT) and HIV-1 group O in the envelope (gp41) regions respectively. These results were consistent with phylogenetic analyses of corresponding sub-genomic regions. Altogether, phylogenetic analysis and similarity profile of the near full length genome sequences showed that both spouses were infected with a unique recombinant virus (M/O) having its recombination breakpoint in the vpr gene.

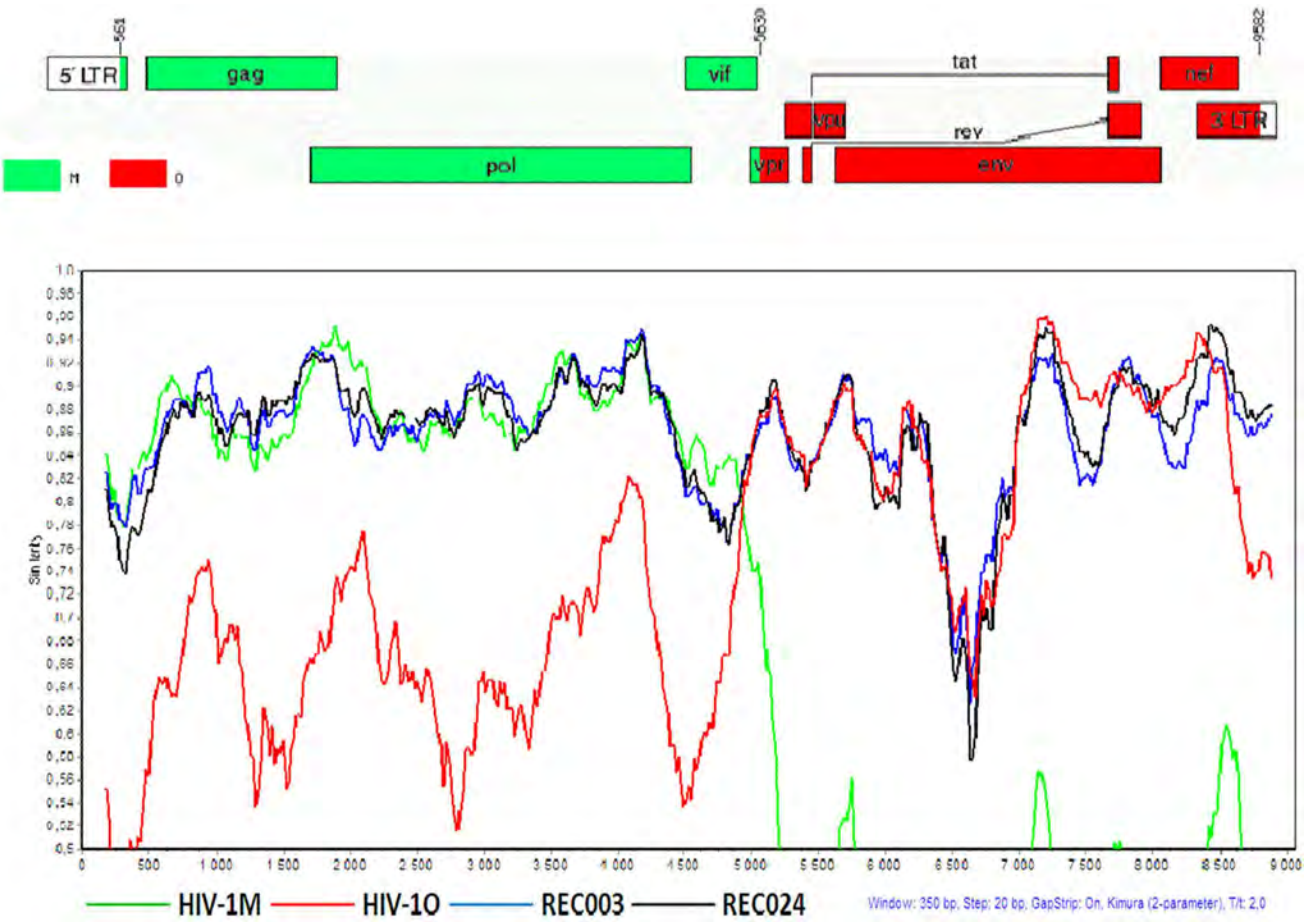


Figure 1: Recombination analyses of REC003 (Husband ; accession no KM438031) and REC024 (Wife; accession no KM438032) viruses

Near full-length genomes of REC003 (9135bp; blue line) and REC024 (9176bp; dark line) were compared each other and with the closest strains of HIV-1 group M (suptype F2; green line) and HIV-1 group O (red line) identified by HIV BLAST. The viruses exhibit a mosaic structure M-O with the gag-pol portion belonging to HIV-1 M and the env portion belonging to HIV-1 O. Both viruses defined the same patterns along the entire genome.

Conclusions: In this study, we observed for the first time that HIV-1 M/O intergroup recombinant viruses could be transmitted from one person to another. The genetic diversity and public health importance of transmitting these recombinant viruses in such areas where both viruses (HIV-1 groups M and O) are endemic cannot be overemphasized.

234 Searching for Rare HIV Strains in Rural Democratic Republic of Congo (2001–2003)

Ana S. Vallari[1]; Carole McArthur[2]; Larry Sthreshley[3]; Catherine Brennan[1]

[1]Abbott Laboratories, Chicago, IL, US; [2]University of Missouri–Kansas City, Kansas City, MO, US; [3]IMA World Health, Kinshasa, Congo (the Democratic Republic of the)

Background: The Democratic Republic of Congo (DRC) is thought to be the epicenter of the HIV/AIDs pandemic. Not only were the oldest documented HIV-1 infections found in Kinshasa (circa 1959-1960) but the many diverse HIV-1 strains circulating in the DRC show high levels of intrasubtype diversity and intersubtype recombination indicative of an old epidemic. In this study, we characterized HIV strains in two rural areas of the DRC to identify and obtain sequences for rare subtypes and recombinants found only in the DRC.

Methods: Specimens were collected, between 2001-2003, at the Vanga Hospital, Bandundu Province and The Good Shepard Hospital located 12 kilometers from Kananga, Kasia-Occidental Province in the DRC. A total of 264 HIV-infected specimens from voluntary testing and pregnant women participating in a PMTCT program were characterized. HIV serotype was determined based on antibody reactivity to HIV type and group specific peptides derived from *env* gp120 V3 loop and gp41 immunodominant region using a multiplex immunoassay. Strain classification was determined by RT-PCR amplification and phylogenetic analysis of the *env* gp41 sequence; for rare subtypes, *gag* and *pol* sequences were also obtained and evaluated.

Results: The peptide serotyping assay classified all infections as HIV-1 group M except for 2 HIV-2 infections. Phylogenetic analysis of 164 *env* sequences showed a high level of strain diversity. Subtype A predominated (43.9%) but 8 additional subtypes and 3 CRFs were found: subtype C (3.0%), D (9.8%), F1 (4.3%), G (12.2%), H (4.3%), J (1.2%), K (0.6%), L (0.6%), CRF01 (6.7%), CRF02 (8.5%), CRF11 (0.6%) plus unclassified (4.3%). Two subtype H, and the subtype J, K and L strains had concordant classification based on *gag*, *pol*, and *env* sequences.

Conclusions: Molecular characterization of HIV-infected specimens collected in the DRC show many different strains are circulating in the population and identified rare HIV subtypes H, J, K, and L for which very limited sequences are currently available. Subtype H, J and K sequences are most frequently found within CRFs thus the potentially pure subtype H, J, K and L strains identified here require confirmation by full genome sequencing. Continued surveillance of HIV strain diversity is important and essential to address the challenge posed by ongoing evolution of HIV and to monitor the rapidly changing HIV pandemic.

235 Clinical and Virological Characterization of CRF07_BC infection

Szu-Wei Huang[1]; Sheng-Fan Wang[1]; Chih-Hao Lee[1]; Wing-Wai Wong[2]; Hung-Chin Tsai[3]; Chia-Jui Yang[4]; Chin-Tien Wang[5]; Jaang-Jiun Wang[6]; Daniel Kuritzkes[7]; Yi-Ming A. Chen[1]

[1]Kaohsiung Medical University, Kaohsiung City, Taiwan; [2]Taipei Veterans' General Hospital, Taipei, Taiwan; [3]Kaohsiung Veterans' General Hospital, Kaohsiung City, Taiwan; [4]Far Eastern Memorial Hospital, New Taipei City, Taiwan; [5]National Yang-Ming University, Taipei, Taiwan; [6]Children's Healthcare of Atlanta and Emory University School of Medicine, Atlanta, GA, US; [7]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, US

Background: The circulating recombinant form (CRF) 07_BC is the most prevalent HIV-1 strain among injection drug users in Taiwan. It contains a 7 amino-acid deletion (7d) in its $p6^{gag}$. The objectives of this study were to conduct a cohort study to compare viral load and CD4 cell count changes between patients infected with subtype B and CRF07_BC and to elucidate its mechanism.

Methods: Twenty-one patients infected with CRF07_BC and 59 patients with subtype B were selected from a cohort of 667 HIV-1/AIDS patients whom have been followed up for more than 3 years. Generalized estimated equation was used for statistical analysis. The replicative kinetics, tropism and cytopathic effects were determined. HIV-1 NL4-3 which containing a 7 amino-acid deletion in $p6^{gag}$ (7d virus) was generated and its virological properties were compared with the wild-type.

Results: Patients infected with CRF07_BC had significantly lower viral load than patients with subtype B. CRF07_BC isolates had lower replicative capacity than subtype B isolates although they were all CCR5 tropic. 7d virus had significantly lower gag processing efficiency and slower viral life cycle. Electronic microscopy showed 7d virus had poorer viral maturation processes: virions attached to the cell membrane were largely immature. The interaction between $p6^{gag}$ and Alix protein was less efficient in cells infected with 7d virus.

Conclusions: Patients infected with CRF07_BC had significantly lower viral loads than patients infected with subtype B. Such phenomenon may be due to the deletion of 7 amino acids which overlap with the Alex protein-binding domain of CRF07_BC virus.

236 Reconstructing the HIV-1 Epidemics in Burkina Faso Using Early Samples

Gonzalo Yebra[1]; Marcia L. Kalish[2]; Andrew J. Leigh Brown[1]

[1]University of Edinburgh, Edinburgh, United Kingdom; [2]Vanderbilt University, Nashville, TN, US

Background: Two HIV-1 recombinants dominate the epidemics in Burkina Faso: CRF06_cpx (first described in this country) and CRF02_AG. Here, we reconstruct the phylodynamics of both epidemics in Burkina Faso and Western Africa using for the first time early sequences from samples taken in 1986 and modern sequences from GenBank.

Methods: The early sequences were 52 protease (PR) and 37 gp41 sequences for CRF06_cpx and 15 PR and 25 gp41 for CRF02_AG; to which we added GenBank sequences (1993-2013). For CRF06_cpx, we analysed all sequences (163 PR / 41 gp41). For CRF02_AG, we analysed Burkina Faso sequences (142 / 39) and, in a second analysis, sequences from Western Africa (380 / 170) and the closest sequences from Central Africa (311 / 128). Owing to the short length of the sequences available, we analysed sequence data for both genes jointly using the BEAST multilocus analysis to improve convergence and confidence intervals on the growth curves. We also conducted a phylogeographic analysis by using the discrete traits analysis implemented in BEAST to reconstruct the main migration routes between countries.

Results: The most recent common ancestor (MRCA) of global CRF06_cpx was 1979 (1977-1980) for both PR and gp41, with respective evolutionary rates of 5.5 (4.8-6.3) $\times 10^{-3}$ substitutions/site/year (s/s/y) and 6.1 (4.8-7.5) $\times 10^{-3}$ s/s/y. The phylogeographic analysis of gp41 showed that CRF06_cpx (or at least its parental subtype G lineage) emerged in the Democratic Republic of Congo (DRC) but arrived soon after (1981) in Burkina Faso. Both PR and gp41 showed that this recombinant radiated to the rest of Western Africa only around 1990. The MRCA of CRF02_AG in Burkina Faso was 1979 (1977-81) for both PR and gp41 with rates of 2.3 (1.8-2.9) $\times 10^{-3}$ s/s/y and 5.7 (4.1-7.4) $\times 10^{-3}$ s/s/y. In West Africa, the phylogenetic trees showed CRF02_AG sequences interspersed regardless of their sampling country, and the phylogeographic analysis showed much interconnection between countries with 3 main transmission hubs in Cameroon, Burkina Faso and Senegal.

Conclusions: Burkina Faso presents a relatively young HIV epidemic, with the two main variants originating around 1980. CRF06_cpx might have emerged in DRC but radiated throughout Western Africa from Burkina Faso. However, CRF02_AG entered Burkina Faso though multiple introductions. Indeed, the CRF02_AG epidemic showed much interchange between Western African countries but also connections with Central Africa, which suggests a great mobility in the region.

237 Neutralizing Antibodies in Humans Infected With Zoonotic Simian Foamy Viruses

Caroline Lambert[1]; Julie Gouzil[2]; Réjane Rua[1]; Edouard Betsem[3]; Antoine Gessain[1]; **Florence Buseyne**[1]

[1]Institut Pasteur, Paris, France; [2]Ecole Vétérinaire, Maison-Alfort, France; [3]University of Yaounde, Yaounde, Cameroon

Background: Simian foamy viruses (SFVs) are efficiently transmitted from non-human primates to humans, establishing persistent infection in the new host. Neither pathogenic effects nor human-to-human transmission have been reported, suggesting that immune control of this retrovirus is efficient. Here, we aimed at studying the humoral response. We used viral strains isolated from animals and infected humans to study the neutralizing antibodies present in the plasma of SFV-infected people living in rural areas of South Cameroon.

Methods: Serial dilutions of plasma samples from 46 SFV-infected individuals and seven uninfected subjects were incubated with SFV. Residual viral infectivity was quantified with an indicator cell line expressing the beta-galactosidase gene under the control of the LTR from the prototypic strain, SFVcpzPFV. Four strains from the chimpanzee clade were used: the SFVcpzPFV and SFVcpzSFV7 strains, from serogroups 6 and 7, respectively, and the SFVcpzBAD327 and SFVcpzAG15 strains, isolated from individuals from our study population.

Results: Plasma samples from the six people infected with SFV from the chimpanzee clade neutralized either SFVcpzPFV or SFVcpzSFV7. Plasma samples from the seven uninfected individuals and the five individuals infected with SFV from small monkeys did not neutralize any SFVcpz strain. In total, 35 people were infected with SFV from the gorilla clade: 21 of these plasma samples neutralized the SFVcpzPFV strain, eight neutralized the SFVcpzSFV7 strain and one neutralized both strains. Neutralizing titers ranged from 1/30 to 1/2060. Five plasma samples did not neutralize any of the strains tested. The titers of neutralizing antibodies against the zoonotic SFVcpzBAD327 and SFVcpzAG15 strains were strongly correlated with the titers of neutralizing antibodies against the SFVcpzSFV7 strain (Spearman's rho=0.998, $P<0.0001$ and rho=0.957 $P<0.0001$, respectively).

Conclusions: SFVs from the chimpanzee and gorilla clades transmitted to humans had similar antigenic properties and belonged to at least two serogroups described in non-human primates. The conservation of the neutralizing epitopes may account for the efficient immune control of these retroviruses. No SFV RNA was detected in the peripheral blood and saliva of these individuals, but the relatively high titers of neutralizing antibodies in some of them suggest that active SFV replication may occur in humans with persistent zoonotic SFV infections.

TUESDAY, FEBRUARY 24, 2015

Session P-B2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Defining Epidemiologically Linked Transmission

238 Large Phylogenetically Linked HIV Cluster in King County, Washington, 2008 to 2014

Susan E. Buskin[1]; Joshua T. Herbeck[2]; Katelynne M. Gardner Toren[1]; Michelle R. Perry[1]; Amy Bennett[1]; Matthew R. Golden[2]

[1]*Public Health—Seattle & King County, Seattle, WA, US;* [2]*University of Washington, Seattle, WA, US*

Background: Core transmission is a basic tenant of sexually transmitted infection (STI) epidemiology—that a few individuals are responsible for a large proportion of STI transmissions. However, relatively little data exist on core transmission for HIV. We present phylogenetic analyses supporting the role of a core transmitter of HIV infection.

Methods: Public Health – Seattle & King County (PH) field services staff identified an individual (index case) diagnosed with HIV infection in 2008 and who was named as a potential transmitting sex partner by 11 different men between 2008 and 2014. We used PH HIV-1 *pol* nucleotide sequences collected by Molecular HIV Surveillance for HIV cases diagnosed 1/08 to 9/14 to assess the phylogenetic relatedness of people naming the index case as a sex partner, and to define the size of the associated transmission cluster.

Results: Phylogenetic data were available for 10 of 12 men identified through field services investigations. Seven of the 10 epidemiologically-linked cases were phylogenetically linked in a cluster of 66 cases; this was the largest subtype B cluster identified in the area, comprising 5% of 1430 sequences analyzed over the period of observation. Of the 66 cluster cases, 7 including the index case were diagnosed in 2008, 5 in 2013, and 3 (to-date) in 2014; the modal year was 2012 with 17 diagnoses. All but 1 case was male, and 94% reported sex with men. All 66 cluster cases had primary high-level non-nucleoside reverse transcriptase (NNRTI) resistance; these 66 are 36% of all NNRTI resistant cases in the time period. Sequences from the 66 cluster cases were collected 0 to 485 days from HIV diagnosis (median 16 days); none had achieved viral suppression prior to specimen collection. A most recent viral load was suppressed (< 200 copies per ml) for 54 individuals (82%). Of the remaining 12 individuals, 5 had > 1 log reduction in viral load (range 1.6 to 3.8), one individual relocated, and the remaining 6 are under investigation but are not known to be virologically suppressed. The index case was not previously virally suppressed, but was successfully relinked to care by PH.

Conclusions: This large cluster of epidemiologically and molecularly-related cases supports the role of core transmission in HIV infection. The ability of field services staff to identify an untreated man who we believe played a central role in this transmission network demonstrates the utility of routine partner services investigations.

239 Reconciling Named Partner and Genetic Partner HIV-1 Transmission Networks in New York City

Joel O. Wertheim[1]; Sergei L. Kosakovsky Pond[1]; Konrad Scheffler[1]; Davey M. Smith[1]; Sanjay Mehta[1]; Sharmila Shah[2]; Lisa Forgione[2]; Lucia V. Torian[2]

[1]*University of California San Diego, San Diego, CA, US;* [2]*New York City Department of Health and Mental Hygiene, New York, NY, US*

Background: The New York City Department of Health and Mental Hygiene (DOH) interviews persons with newly diagnosed HIV infection (index cases) and elicits partners, who are notified of exposure and offered HIV testing. When resistance testing is ordered by a physician with whom the case or positive partner has initiated care, the viral nucleotide sequence is reported to surveillance.

Methods: Between 2006 and 2012, DOH interviewed 770 index cases with genotypes; these cases named 810 HIV+ partners with genotypes, for a total of 1,369 cases linked to named partners (211 index cases were also named by other index cases). Using *pol* sequences, we identified index and named partners who were closest relatives in a maximum likelihood phylogeny. We then estimated the Tamura-Nei 93 (TN93) genetic distance between each pair of index cases and named partners. We designated viral sequence pairs that fell below a validated distance cutoff of 1.75% as genetic links. Our data made it possible to construct two networks: the network of cases and their named partners (the named partner network; N=1,369) and the network of clusters of persons genetically linked by their TN93 distance (the genetic partner network; N=862 [63% of the 1369 cases]). We examined the degree of overlap between the two networks. We used logistic regression to assess the variables associated with the index case successfully naming at least one genetically linked partner.

Results: 451 of 770 (59%) index cases named partners who were also genetically linked (Table). Heterosexual female index cases were more likely to be genetically linked to a named partner (77%) than men who have sex with men (42%, OR=0.21, 95% CI 0.14, 0.31) and male injecting drug users (38%, OR=0.18, 95% CI 0.08, 0.38). Black index cases were less likely than whites and Hispanics to name a genetically linked partner (53%, OR=0.46, 95% CI 0.25, 0.87). In the named partner network, 747 out of 1,369 (55%) cases were genetically linked to a named partner, whereas in the genetic network, 720 out of 862 (84%) persons were genetically linked to a named partner.

Logistic regression analysis of FSU index partner being genetically-linked to at least one of their named partners (n = 770 index partners).

Demographic	Category[1]	Total	Named ≥ 1 genetically linked partner	Did not name a genetically linked partner	% with genetically linked partner	Odds Ratio[2]	95% confidence interval	p-value
Total	-	770	451	319	-	-	-	-
Risk	Hetero (F)	218	167	51	77%	1	-	-
	Hetero (M)	93	72	21	77%	1.14	0.62–2.07	0.677
	MSM	343	143	200	42%	0.21	0.14–0.31	>0.001
	IDU (F)	15	8	7	53%	0.38	0.13–1.13	0.083
	IDU (M)	39	15	24	38%	0.18	0.08–0.38	>0.001
	Other/Unknown	62	46	16	74%	1.04	0.54–2.03	0.904
Race[3]	White	55	32	23	58%	1	-	-
	Black	398	211	187	53%	0.46	0.25–0.87	0.016
	Hispanic	311	208	103	67%	0.92	0.48–1.78	0.810

Hetero, heterosexual; MSM, men who have sex with men; IDU, injecting drug user

[1]Demographic categories reflect index case partner only.
[2]Model adjusted odds ratio. Variables not significantly associated with linking (i.e. country of birth, subtype, diagnosis status, AIDS status, and age) are not shown.
[3]Only whites, blacks, and Hispanics had sufficient numbers for display

Conclusions: Construction of genetic transmission networks can supplement partner naming by identifying previously unknown parts of a potential transmission network, i.e., unnamed partners. If real-time genotyping coupled with network analysis can be implemented, it can be used to interdict ongoing transmission and to improve epidemic control.

240 Efforts to Characterize Community HIV Transmission Dynamics May Be Critically Dependent on Provision of Both Partner Services and Genetic Sequence Analysis

Nella L. Green; Christy Anderson; Sergei L. Kosakovsky Pond; Martin Hoenigl; David M. Smith; Sanjay Mehta; Susan Little

University of California San Diego, San Diego, CA, US

Background: Genetic analysis of HIV-1 sequences has become the gold standard for inferring HIV transmission networks. However, the added value of epidemiological links supplied via partner counseling and referral services (PCRS) is unclear.

Methods: We examined bulk *pol* sequence and epidemiological data from the San Diego Primary Infection Resource Consortium (PIRC) collected between 1996 and 2013. PCRS services were routinely provided to recently HIV infected persons to characterize epidemiologically linked partnerships (named partners). Two individuals whose nucleotide HIV-1 sequences differed by at most 1.5% (Tamura-Nei 93 distance) were considered genetically linked. We compared two types of putative transmission pairs: Group 1: genetically and epidemiologically linked, and Group 2: genetically, but not epidemiologically linked.

Results: 591 newly HIV infected persons were identified in the PIRC cohort. Provision of PCRS yielded 184 epidemiologically linked partnerships, of which 52 (28%) were also genetically linked (Group 1). Of the remaining 132 partnerships, 93 were linked to HIV-negative individuals and 39 (21% of total) were linked to HIV-infected persons whose genetic sequences differed. Sequence analysis alone identified 459 dyads (i.e. Group 2). 337 individuals made up the 511 pairs (Groups 1 + 2) included in this analysis. There were no significant differences comparing dyad concordance between Groups 1 and 2 with regard to race, ethnicity, income, CD4, viral load, and recent or current sexually transmitted infections. Partner age differences were greater in Group 2 ($p = 0.012$). The elapsed time between identification of the index and their linked partner was significantly different ($p<0.001$) between groups (Group 1 median 15 days [IQR 7-46 days]; Group 2 median 532.5 days [IQR 222-1194 days]).

Conclusions: Sequence analysis and PCRS may identify a uniquely different population than that identified with sequence analysis alone. As expected, only a minority (28%) of PCRS pairs were corroborated by genetic data, yet these partnerships yielded a more rapid linkage identification (15 days vs 532 days) and also captured individuals more similar in age, as compared to partnerships identified solely by genetic analysis. We conclude that the primary and valuable benefit of PCRS is to yield recently connected putative transmission pairs that may represent more attractive targets for interventions and are more likely to represent direct transmission events.

WEDNESDAY, FEBRUARY 25, 2015

Session P-B3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Transmission Clusters

241 Growth and Geographic Spread of HIV Transmission Clusters, United States, 2007-2012

Alexandra M. Oster[1]; Joel Wertheim[2]; Ellsworth Campbell[1]; Angela L. Hernandez[1]; Neeraja Saduvala[2]; William M. Switzer[1]; M. Cheryl Ocfemia[1]; Anupama Shankar[1]; H. Irene Hall[1]

[1]US Centers for Disease Control and Prevention (CDC), Decatur, GA, US; [2]ICF International, Atlanta, GA, US

Background: Molecular epidemiology can be used to identify clusters of persons with genetically related viruses. Clusters that continue to grow over time likely represent ongoing transmission and are potential points for intervention. Predicting which clusters are likely to grow could guide the appropriate allocation of limited prevention resources toward ensuring viral suppression and stemming transmission.

Methods: We aligned HIV-1 sequences (1/person) reported to the U.S. National HIV Surveillance System to a reference sequence, conducted pairwise comparison of 70,669 sequences, and constructed an HIV transmission network of sequences with Tamura-Nei genetic distance ≤1.5%. We used HIV diagnosis year to construct the network over time and assess changes during 2007–2012. For clusters with ≥5 persons in 2007, we characterized growth through 2012 and used multivariable logistic regression to examine potential predictors of various levels of growth, including cluster size in 2007, cluster growth from 2006 to 2007, and demographic/risk characteristics. Finally, we described geographic characteristics of the largest clusters.

Results: From 2007 to 2012, the number of persons with sequences and the number of clusters grew substantially (Table). In 2007, 177 clusters contained ≥5 persons. By 2012, these 177 clusters grew 235% overall, from 1,492 to 3,500 persons. Twenty-nine (16%) clusters grew ≥200% during 2007–2012, representing 54% of growth among clusters of ≥5 persons. Clusters that grew ≥200% did not differ from clusters that grew <200% with respect to size in 2007, growth from 2006 to 2007, racial/ethnic makeup, or the percentage of men who have sex with men (MSM). However, higher percentage of persons aged 13–19 years was associated with growth ≥200% ($p=0.048$). Growth ≥100% (n=76 clusters) was associated with rate of cluster growth from 2006 to 2007 ($p=0.01$) and higher percentage of MSM ($p=0.04$). Of the 8 largest clusters (size=79–155 in 2012), 5 consisted nearly exclusively (>90%) of persons living in the same state at diagnosis, one included persons from 7 Southern states, and two included persons from across the United States.

	2007	2012
No. of persons with sequences	36,947	70,669
No. (%) of persons who clustered	4,667 (13%)	21,117 (30%)
Number of clusters	1,520	5,336
Size of largest cluster	65	155

Characteristics of HIV transmission clusters, 2007 and 2012

Conclusions: We found substantial growth of clusters over a 5-year period. The best predictors of cluster growth ≥100% were growth in the previous year and the percentage of MSM. Rapid growth (≥200%) was best predicted by the percentage of adolescents. These data suggest that monitoring the growth and composition of clusters can help to identify prevention priorities.

242 HIV Transmission Networks Among the USA, Mexico, and Central America

Santiago Avila-Rios[1]; Joel O. Wertheim[2]; Ann M. Dennis[8]; Gustavo Reyes-Terán[1]; Carlos Mejía-Villatoro[3]; Elsa Y. Palou[4]; Guillermo Porras-Cortes[6]; Juan M Pascale[5]; Marvin Manzanero[7]; Sanjay Mehta[2]

[1]National Institute of Respiratory Diseases, Mexico City, Mexico; [2]University of California San Diego (UCSD), San Diego, CA, US; [3]Roosevelt Hospital, Guatemala City, Guatemala; [4]Hospital Escuela Universitario, Tegucigalpa, Honduras; [5]Gorgas Memorial Institute for Health Studies, Panama, Panama; [6]Vivian Pellas Metropolitan Hospital, Managua, Nicaragua; [7]Ministry of Health, Belmopan, Belize; [8]University of North Carolina, Chapel Hill, NC, US

Background: The role of migration in shaping genetic diversity of viral populations has been well established. We show results of a large collaborative effort to assess epidemiological networks and dispersion routes between the HIV epidemics in the United States, Mexico and Central America, including Guatemala, Belize, Honduras, El Salvador, Nicaragua and Panama.

Methods: We analyzed 7943 HIV-1 *pol* sequences collected from Mexican and Central American national HIV sequence databases, and local databases located at the University of North Carolina and the University of California, San Diego. These sequences were aligned to the reference sequence HXB2. We then estimated Tamura-Nei (TN) 93 pairwise genetic distances among all sequences. Sequences that were ≤1.5% TN93 distance divergent were deemed similar enough to be potential transmission partners. We then constructed transmission clusters by linking sequences through shared potential transmission partners.

Results: In total, 2349 (30%) of sequences had a potential transmission partner in the network, comprising 846 distinct transmission clusters (range 2-53 members). Twenty five (3.0%) of these clusters included sequences isolated from at least two individuals in different countries, and six clusters included sequences isolated from both San Diego and North Carolina. Fourteen clusters included linkages between sequences isolated in San Diego and in Mexico. North Carolina sequences were linked to sequences from Guatemala in three clusters, Panama in two clusters and Mexico in two clusters; nearly all these sequences were from Latino immigrants. Below is a figure depicting all of the clusters identified in this analysis with nodes shaded by country of origin.

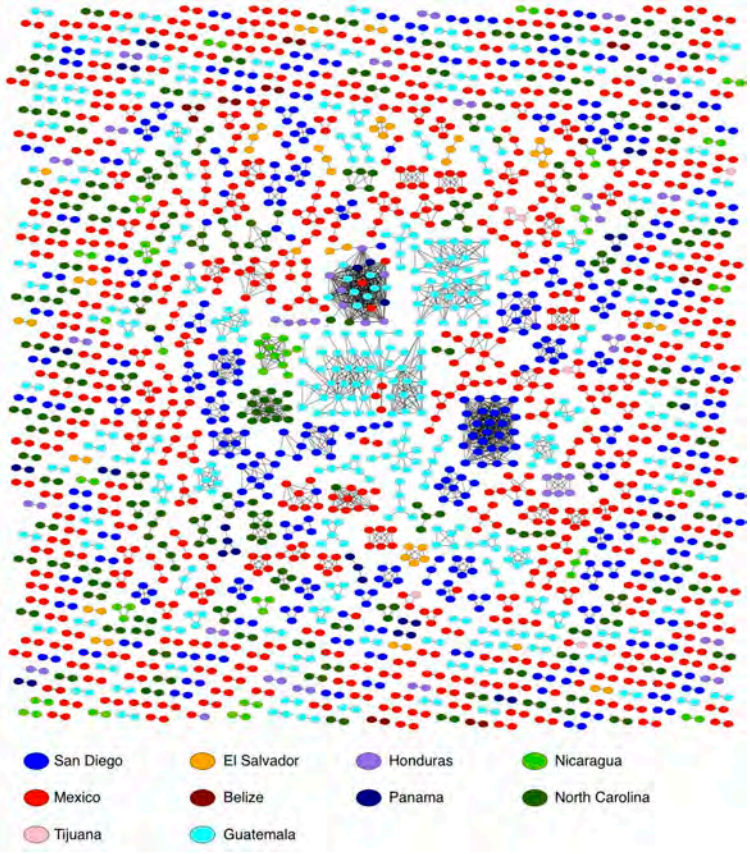


Figure 1. HIV transmission clusters in the USA, Mexico and Central America. Tamura-Nei 93 pairwise genetic distances were estimeted among 7943 pol sequences and clusters were constructed by linking sequences through shared potential transmission partners. Only sequences forming clusters are shown. Each node represents a single sequence colored by geographic region.

Conclusions: Our work underlines the importance of political and cultural barriers in HIV transmission among the USA, Mexico and Central America, with most transmission events occurring within countries. Nevertheless, the presence of some international connections was observed, reflecting possible important events influencing HIV diversity in the region. Continued network analyses have the potential to inform transnational HIV prevention efforts.

243 Sexual Networks Across Risk Groups Persistently Contribute to Local Spread of HIV

Marije Hofstra[1]; Tania Mudrikova[1]; Marieke Pingen[1]; Kristine Koekkoek[1]; Arjan Van Laarhoven[1]; Rob Schuurman[1]; Andy I. Hoepelman[1]; Annemarie M. Wensing[1]

[1]University Medical Center Utrecht, Utrecht, Netherlands; [2]University Medical Center Utrecht, Utrecht, Netherlands

Background: Despite the sharp drop in influx of immigrants from HIV endemic countries since 2003, HIV incidence is not decreasing in the Netherlands. This could be due to increased testing and/or increased incidence among the native Dutch population. Therefore we aimed to get insight in local transmission dynamics.

Methods: In 2004-2013, 709 adults newly diagnosed with HIV presenting at the University Medical Center Utrecht participated in the local Athena cohort. *Pol* sequences of 663 (94%) therapy-naive patients were aligned with 212 *pol* sequences of therapy-experienced patients from the same period. A neighbor-joining phylogenetic tree was constructed (evolutionary model Tamura-Nei, 1000 replicates, MEGA6). Transmission clusters were identified using a threshold of bootstrap support of 95% and genetic distance <0.015. Subtyping was performed using COMET v0.5.

Results: Of all newly diagnosed patients, the majority (84.9%) was male with a mean age of 39 years. MSM was the main route of transmission (65.6%), followed by heterosexual contact (HSX; 27.2%) and IV drug use (0.8%). The majority was of Dutch ancestry (73.9%), 11.6% was originating from sub Saharan Africa and 14.5% from other regions. Half of the newly diagnosed patients (53.4%) were part of a transmission cluster. We identified 19 large clusters (6-23 patients, n=193): 1 subtype C cluster of 18 patients of Dutch origin (11 MSM, 2 female HSX, 3 male HSX, 2 unknown), 1 subtype A1 cluster of 8 patients of Dutch origin (5 MSM, 1 male HSX, 2 female HSX) and 1 subtype CRF02_AG cluster of 6 MSM patients of mixed origin. The other 16 large clusters were all subtype B, of which 11 clusters consisted only of patients of Dutch ancestry. Six clusters included both MSM and male HSX and 1 cluster MSM and female HSX. Using prior negative HIV test results, the mean persistence of these clusters was at least 48 months, with a range from 10 to 82 months. The non-B subtypes have been circulating for at least 33 (CRF02_AG), 36 (A1) and 75 (C) months.

Conclusions: Half of the newly diagnosed HIV patients were part of a local cluster that persisted for up to nearly 7 years, suggesting local transmission highly contributes to the HIV epidemic in the area. Longstanding clusters of non-B subtypes are seen in patients of Dutch origin transcending different risk groups.

244 Estimation of HIV-1 Transmission During Recent Infection in Switzerland

Alex Marzel[1]; Mohaned Shilaih[1]; Wan-Lin Yang[1]; Jürg Böni[2]; Sabine Yerly[3]; Thomas Klimkait[4]; Vincent Aubert[5]; Huldrych F. Günthard[1]; Roger Kouyos[1]
On behalf of the Swiss HIV Cohort Study (SHCS)

[1]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland; [2]Swiss National Center for Retroviruses, Zurich, Switzerland; [3]Laboratory of Virology, Geneva, Switzerland; [4]Department of Biomedicine–Petersplatz, Basel, Switzerland; [5]Division of Immunology and Allergy, Lausanne, Switzerland; [6]The Swiss HIV Cohort Study, Zurich, Switzerland

Background: Knowing the fraction of transmissions attributable to recent HIV infections is essential for the success of Treatment-as-Prevention. This is because recently infected patients are often unaware of their HIV status and hence remain untreated and highly infectious.

Methods: A maximum-likelihood phylogeny was constructed from 121,306 HIV-1 pol sequences (21,471 sequences from 11,567 Swiss HIV Cohort Study (SHCS) participants and 99,835 sequences from the Los Alamos database). Swiss transmission clusters were identified using different combinations of intra-cluster genetic distance (1%, 1.5%, 2%, 2.5%) and bootstrap (50% to 100% by increment of 2%) thresholds, in order to determine the effect of those criteria. Seroconversion dates were estimated based on immunological markers, dates of HIV positive/negative tests, clinical symptoms and ambiguous nucleotides. Transmission clusters were classified as recent or chronic transmission based on the maximal time interval between the seroconversion dates of the cluster members. Logistic regression with adjustment for age, sex, risk group, HIV subtype, baseline RNA/CD4, time-to-ART and Chronic phase RNA viral load integral, was applied to identify, among transmitters, the risk factors associated with having transmitted in the recent or chronic phase.

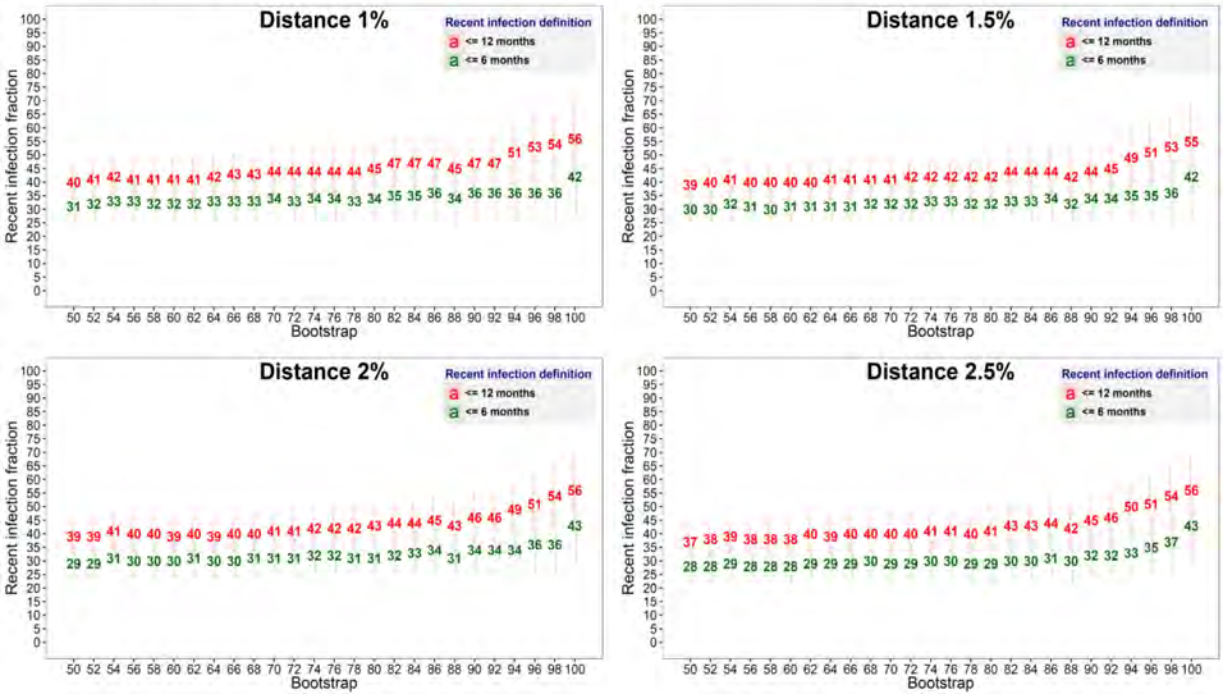
Results: Depending on the implemented phylogenetic threshold criteria, we identified between 50 to 271 transmission clusters with known seroconversion dates for all members. These clusters showed that:

1. The median fraction of transmission during recent infection was 42.2% (range 37%-56%) when recent infection was defined as the first year of the infection and 32% (range 28%-43%) for a six months definition.

2. Stricter criteria for defining transmission cluster (higher bootstrap thresholds) were strongly associated with higher fractions of recent phase transmission, Figure 1, (Spearman`s rho 0.95, P <0.001).

3. The total viral load in the chronic phase (measured as the Chronic phase RNA viral load integral) was negatively associated with recent as opposed to chronic phase transmission, OR 0.43 (0.24-0.77). This effect was even stronger in the adjusted model OR 0.25 (0.1-0.67).

Figure 1. Estimation of HIV-1 transmission during recent infection in the SHCS, by varying phylogenetic thresholds for a definition of transmission cluster. Numbers in red represent recent transmission fraction according to a definition of twelve months for recent infection. Numbers in green represent recent transmission fraction according to a definition of six months for recent infection. Vertical lines represent 95% confidence intervals for proportion.



Conclusions: Our data points to a high fraction of transmission during recent HIV infections in the SHCS. Moreover, we show that the total viral load in the chronic phase is a strong determinant of the transmission phase. These results are important to the pertinent debate on Treatment-as-Prevention as an "Endgame" strategy.

245 Clustering of Swiss HIV Patients Not Enrolled in the Swiss HIV Cohort Study (SHCS)

Mohaned Shilaih[1]; Alex Marzel[1]; Jörg Schüpbach[1]; Jürg Böni[1]; Sabine Yerly[2]; Thomas Klimkait[4]; Vincent Aubert[3]; Huldrych F. Günthard[1]; Roger Kouyos[1]
The Swiss HIV Cohort Study (SHCS)

[1]University Hospital Zurich, Zurich, Switzerland; [2]Geneva University Hospital, Geneva, Switzerland; [3]University Hospital Lausanne, Lausanne, Switzerland; [4]University of Basel, Basel, Switzerland; [5]University of Zurich, Zurich, Switzerland

Background: One of the central challenges in HIV surveillance is that the surveyed population might not be representative of the entire HIV-infected population, especially with respect to marginalized populations. The SHCS is exceptionally representative (75% of HIV patients on ART), however the possibility remains that entire sub-epidemics might be missed by the cohort. A unique opportunity to assess the presence of such "under the radar" populations is provided by a database of all genotypic resistance tests performed in Switzerland, which includes both cohort and non-cohort patients.

Methods: Phylogenetic cluster analysis was used to assess the presence of a hidden sub-epidemic. 11338 SHCS and 3099 Swiss non-SHCS sequences were pooled with 27803 background sequences from the Los Alamos database (10 best BLAST hits for each Swiss sequence). A maximum likelihood phylogenetic tree was built using FastTree. Clusters that were dominated by Swiss sequences (>=80%) were interpreted as Swiss transmission clusters.

Results: Non-B subtypes were strongly overrepresented in the non-SHCS compared to the SHCS (OR 3.0, 95%CI 2.8-3.3). Moreover, non-SHCS patients were more likely to be female (OR 1.4, 95%CI 1.3-1.6). Transmission groups were assigned to non-cohort sequences based on phylogenetic proximity. This revealed that heterosexuals were more present among non-SHCS patients (OR 2.0, 95%CI 1.8-2.2; compared to MSM). Associations remained significant after adjusting for sex, test date, and subtype.

We found 301 transmission clusters purely of non-SHCS patients. However, these clusters were small (median 4.5, IQR 3.25-5.75, max 9) compared to those consisting only of SHCS patients (median 7.5, IQR 4.75-10.2, max 17). Non-SHCS patients were more likely to be part of a transmission cluster compared to SHCS patients (OR 1.9, 95% CI 1.8-2.1). However, when sample date was included in the logistic regression model said clustering preference of non-SHCS markedly decreased (1.1, 95%CI 0.99-1.2).

Conclusions: In this work we evaluated the coverage of the SHCS, one of the most representative HIV cohorts. We found an overrepresentation of non-B subtypes among non-SHCS patients suggesting that migrants might be underrepresented in the SHCS. We also observed transmission chains among non-SHCS patients, yet their limited size and frequency suggest that no major HIV outbreak in Switzerland is missed by the SHCS. More generally, this work shows the potential of sequence data to assess the representativeness of cohort studies.

246 HIV Transmission Network Structure Reveals Characteristics of Bridging Individuals

Sanjay Mehta; Joel O. Wertheim; Konrad Scheffler; Susan Little; Richard R. Garfein; Sergei L. Kosakovsky Pond; David M. Smith

University of California San Diego, La Jolla, CA, US

Background: Molecular epidemiology is often the only means to reveal difficult-to-measure patterns of HIV transmission in local epidemics. Of particular interest are "bridge" individuals that link otherwise disconnected network components, evaluated here for the inferred San Diego Primary Infection Cohort (SDPIC) HIV transmission network.

Methods: We inferred a molecular transmission network (MTN) from a curated collection of 1024 partial *pol* sequences, representing 713 SDPIC participants sampled between 1996 and 2013, and 311 sequences from area chronically infected individuals. Two individuals (nodes) were linked if their sequences were <1.5% distant (TN93 metric). Network degree, mean path length (MPL), and betweenness centrality were computed for each network node, and statistical analyses were used to examine which sociodemographic factors associated with network properties. We also investigated the association of a novel "uniqueness" score with the various measures of network centrality. This score combined the demographic attributes of age, race, ethnicity, HIV risk factor, and location of residence into a single score, which was then used to compare all of the individuals within each transmission cluster relative to one another.

Results: 42.1% of individuals in our study were linked to at least one other individual in the MTN. Age of individuals was the only sociodemographic measure marginally associated with centrality in univariate analyses [p=0.053, age vs clustering, t-test]. In clusters comprising 4 or more individuals, central nodes (low MPL) were significantly more likely [p=0.05, Fishers Exact Test] to have higher uniqueness scores, and the highest scoring individuals had significantly higher betweenness centrality [25.6% vs 8.2%, p=0.041, t-test].

Conclusions: In models of epidemiologic spread, individuals who serve as bridges between otherwise disconnected groups have been implicated as important drivers of HIV epidemics. Our analyses demonstrate in the San Diego HIV epidemic, bridging individuals were sociodemographically unique. Such uniqueness represents a higher degree of disassortative mixing by these key individuals, suggesting that disassortative partnerships may disproportionately drive HIV epidemics.

247 Phylodynamic Analysis of HIV Sub-Epidemics in Mochudi, Botswana

Vladimir Novitsky[1]; Denise Kuehnert[2]; Sikhulile Moyo[3]; Erik van Widenfeldt[3]; Lillian Oku[3]; Max Essex[1]

[1]Harvard School of Public Health, Boston, MA, US; [2]ETH Zürich, Zürich, Switzerland; [3]Botswana-Harvard AIDS Institute Partnership, Gaborone, Botswana

Background: The rapid intrinsic evolution of HIV-1 makes it possible to infer epidemiologic patterns from sequence data. The Bayesian birth-death skyline (BDSKY) plot was introduced recently as a model of virus transmission. We used BDSKY to estimate the effective reproductive number, *R*, and the timing of virus transmission, to distinguish "acute" HIV sub-epidemics (*with* recent viral transmissions) from "historic" sub-epidemics (*without* recent viral transmissions) in a southern-African community.

Methods: Study subjects participated in enhanced household-based HIV Testing and Counselling in Mochudi, a peri-urban village in Botswana. The sampling density was around 70%. HIV-1C V1C5 sequences were generated for 1,248 residents of Mochudi. HIV-1C sub-epidemics were identified by a combination of bootstrapped maximum likelihood and internode certainty. For HIV sub-epidemics with 5+ members, the epidemiological parameters were inferred from virus sequence data. The time line for each sub-epidemic was estimated by fitting the BDSKY model and inferring the tree height and internal node ages in the Maximum Clade Credibility time-trees using BEAST2. For each sub-epidemic we estimated the time interval the majority of HIV transmissions occurred in, with corresponding 95% HPD intervals.

Results: We employed the BDSKY model to estimate effective reproductive number *R* and timing of HIV-1C transmissions within 15 sub-epidemics with 5+ members. Only three of the 15 sub-epidemics were estimated as "acute" with recent HIV transmissions. The median estimates of *R* were 0.7–1.6. The V1C5-based informativeness of *R* estimates differed across sub-epidemics. The median peak duration of viral transmissions was 5.4 years (95% HPD, 3.8 to 8.6 years). The median life span of identified HIV sub-epidemics, i.e., the time from the cluster's origin to its most recent sample, was 14.2 years (95% HPD, 9.8 to 16.4 years). The majority of viral transmissions within 15 identified HIV sub-epidemics in Mochudi occurred between 1997 and 2005. The generated data suggests that the time period during which infected people are infectious has decreased significantly since the introduction of ART in Botswana as the national program.

Conclusions: Viral sequence data from a densely sampled community in Botswana allowed us to estimate the effective reproductive number, *R*, and timing of virus transmissions in 15 local HIV sub-epidemics. "Acute" sub-epidemics with recent HIV transmissions are likely to fuel local HIV/AIDS epidemics.

248 Exploring Transmission Dynamics of HIV in Rural KwaZulu-Natal, Using Phylogenetics

Eduan Wilkinson[1]; Siva Danaviah[1]; Justen Manasa[1]; Frank Tanser[1]; Kobus Herbst[1]; Deenan Pillay[2]; **Tulio de Oliveira**[1]
On behalf of the PANGEA_HIV Consortium
[1]*University of KwaZulu-Natal, Durban, South Africa;* [2]*University College London, London, United Kingdom*

Background: Despite antiretroviral rollout, HIV incidence remains high in South Africa. We have observed significant social and geographical heterogeneity in HIV incidence in rural KwaZulu-Natal (Tanser et al. Science 2013). We sought to utilise phylogenetics to better understand the drivers of ongoing transmission in this hyperendemic population. Further, we explore the utility of sampling a fraction of infections to discern changes in incidence, through phylodynamic approaches.

Methods: Viral load was measured in on 2,420 dried blood spots (DBS) testing positive in the population-based surveillance of 2011 and 2012. 749 partial HIV-1 *pol* gene sequences were obtained from DBS samples with a viral load (VL) >10,000. 900 samples were targeted for genotyping (86.0% success rate). Sequences were analysed against all reference strains from South Africa and manually edited prior to phylogenetic inference. The inferred phylogenies were analysed to identify clusters of low genetic diversity (≤ 0.05) corresponding to transmission clusters/pairs, defined by branch support > 98.0%. Clinical, demographic, socio-economic and geographic characteristics of infected individuals were analysed against identified clusters to discern traits associated with transmission. Molecular clock and coalescent analyses were performed in a Bayesian framework order to identify the origin of the clusters and the rate of expansion of the epidemic.

Results: A total of 54 transmission clusters were identified containing 91 women and 37 men. The mean size of clusters was 2.39 (variation 2 - 13). The mean age of women in clusters was 31.55 years and of men, 35.91 years. 24.8% of individuals within the genotypic clusters were recently infected though they comprise approximately 5 % of the cohort. GIS results support the scenario of 'hotspots' of transmission, while coalescent analyses provide further evidence that HIV incidence is decreasing in this population.

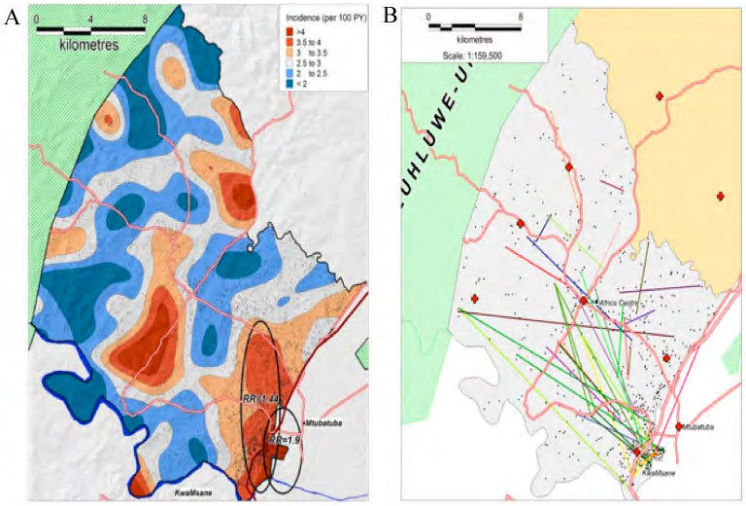


Figure: A) We have used spatial analytical techniques to demonstrate substantial heterogeneity in the epidemic. In terms of HIV-incidence, two high-risk, overlapping spatial clusters were identified in peri-urban communities near the national road. Although the clusters comprise just 5.7% of the study area, they account for nearly one out of every three sero-conversions observed. B) We used genomics data to link HIV-1 infections. The majority of the linkages point to the previously identified hotspots suggesting that those are driving transmission to other areas. Dots represent genotyped individuals. Lines represent linkage.

Conclusions: These results demonstrate the underling complex nature of the dynamics of HIV transmission and that acutely infected patients may disproportionately contribute towards transmissions in the era of increase ARVs. The use of genotypic data coupled with detailed patient information can be used to identify and characterise HIV transmission events. The use of genotypic data analysed within a phylodynamic framework also reflects the decreasing trends in incidence likely due to the scale-up of treatment coverage in recent years.

249 Detecting Changes in Incidence Using Phylogenetic Tools: Simulation-Based Studies Within the PANGEA_HIV Initiative

Emma B. Hodcroft[1]; Oliver Ratmann[2]; Anne Cori[2]; Mike Pickles[2]; Samantha Lycett[3]; Manon L. Ragonnet-Cronin[1]; Matthew Hall[1]; Andrew J. Leigh Brown[1]; Christophe Fraser[2]
On behalf of the Pangea_HIV Consortium
[1]*University of Edinburgh, Edinburgh, United Kingdom;* [2]*Imperial College London, London, United Kingdom;* [3]*University of Glasgow, Glasgow, United Kingdom*

Background: PANGEA_HIV (Phylogenetics and Networks for Generalised HIV Epidemics in Africa) will generate a large volume of next generation viral sequence data from generalized HIV epidemics in sub-Saharan Africa in order to better characterize these epidemics and evaluate HIV prevention efforts. However, the accuracy and reliability of phylogenetic tools to measure aspects of transmission dynamics in these settings is not known.

Methods: The PANGEA_HIV methodology working group conducted a methods comparison exercise in collaboration with multiple, independent research groups to identify the accuracy and power of phylogenetic methods in estimating recent changes in HIV incidence. Two, highly detailed, agent-based epidemiological models capturing generalized HIV transmission dynamics in a village-like, and regional population were developed. Simulated subtype C phylogenies were generated from the transmission tree output which was selected to represent populations varying in HIV incidence dynamics, population size, sampling fraction and model assumptions. Sample datasets of up to several hundred sequences of gag, pol and env for each individual sampled have been generated. These will be coded before distribution to participating collaborators.

Results: First analyses of simple simulated datasets have been performed on pol sequences using a recently developed automated tool ("CPT") which identifies sequence clusters at a maximum genetic distance of 4.5% and bootstrap support of 90%. The samples analysed came from the village model sampled in growth phase (~25 yr post introduction, 4% incidence) and decline (3 yrs after introduction of ART, 2% incidence), with a 20% sampling density. The CPT detected a highly significant decrease in mean cluster size (from 4.13 to 2.76, $p = 0.002$) and an increase in normalised cluster maximum genetic distance (0.0076 to 0.011, $p < 1 \times 10e\text{-}4$), along with a highly significant increase overall in branch lengths (Fig 1).

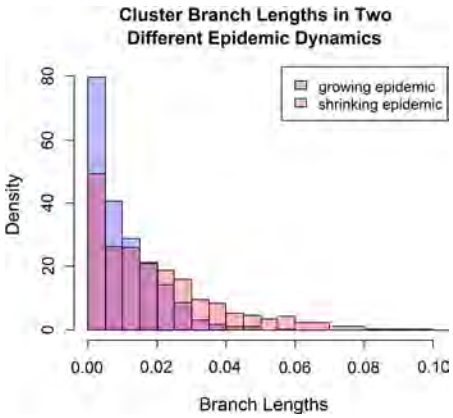


Figure 1 - The mean branch lengths of clusters in a simulated growing epidemic (blue) and simulated shrinking epidemic (pink). The clusters in the shrinking epidemic had a highly significant increase in overall branch length ($p < 2x10e-16$).

Conclusions: We have generated simulated data sets of viral sequences corresponding to samples from hypothetical, generalized HIV-1 epidemic scenarios in sub-Saharan Africa. Initial results show the power of phylogenetic tools to detect changes in incidence and prevalence in the context of generalized HIV epidemics. Further development will focus on using the simulations to test the sample density required by different methodologies to reveal underlying changes in epidemic dynamics.

TUESDAY, FEBRUARY 24, 2015

Session P-B4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Transmission Networks: MSM

250 HIV Transmission Among Seattle Adolescents

Joshua Herbeck[1]; Elizabeth Wolf[1]; Stephen van Rompaey[2]; Mari M. Kitahata[2]; Lisa Frenkel[1]

[1]University of Washington, Seattle, WA, US; [2]Center for AIDS Research, Seattle, WA, US

Background: Phylogenetic analyses of HIV gene sequences can be used to infer putative transmission clusters, with associated individual characteristics used to identify risk factors for HIV transmission. We hypothesized that HIV-infected adolescents would be linked to clusters of infected adults.

Methods: Data from time of first HIV genotyping for drug-resistance, including demographics (age, sex, race), HIV transmission risk (men who have sex with men (MSM), MSM & intravenous drug use (IDU), IDU, heterosexual), and homelessness were obtained from the University of Washington (UW) HIV Information System and retrospective chart review. HIV *pol* sequences were obtained from the UW Clinical Virology Laboratory. Phylogenetic clusters were defined as sequences with a shared ancestral node, support values >95% and pairwise genetic distances ≤0.015 nucleotide substitutions per site. The characteristics of all individuals found in clusters were compared to those of non-clustering individuals using multivariable logistic regression. This process was repeated for clusters with ≥1 adolescents (defined at age 13-24 year at first genotyping).

Results: There were 3116 total HIV-1 *pol* sequences from 1960 individuals, including 115 adolescents, genotyped between February 1, 2000 and March 1, 2013. Fifty-four phylogenetic clusters (containing 169 individuals) were identified. In unadjusted analyses, significant associations existed between cluster membership and adolescent age, MSM, and MSM&IDU. In adjusted analyses including transmission risk group, sex, homelessness, and age class at sequencing (adolescent or adult), adolescent age, MSM and MSM&IDU remained significantly associated with cluster membership.

Fifteen clusters were identified that included ≥1 adolescent; adolescents were 75% male, 57% MSM, 7% IDU, and 12% MSM&IDU. Considering those individuals in these clusters that were not adolescents (i.e. individuals that were adults), there was a non-significant positive association between MSM risk group (adults) and cluster membership.

Conclusions: This study suggests that MSM and MSM&IDU adolescents are at particularly high risk of HIV infection and may require specialized HIV prevention services.

251 Characterization of Large Cluster Viral Networks Sustaining the Montreal MSM Epidemic

Bluma Brenner[2]; Ruxandra-Ilinca Ibanescu[2]; Daniela Moisi[2]; Isabelle Hardy[3]; Jean-Pierre Routy[1]; Joanne Otis[4]; Mark Wainberg[2]; Michel Roger[3]

[1]McGill University, Montréal, Canada; [2]Lady Davis Institute, Montreal, Canada; [3]Université de Montréal, Montreal, Canada; [4]UQAM, Montreal, Canada

Background: This study combined phylogenetic, molecular recency, virological and behavioral data to identify key determinants favoring the ongoing genesis of large viral lineages sustaining the Montreal Men having Sex with Men (MSM) epidemic despite widespread antiretroviral therapy coverage and population declines in viral load.

Methods: Phylogenetic analysis ascertained the genetic interrelatedness of MSM viral sequences (2002-2013), first genotyped in primary HIV infection (PHI, 0-6 months, n= 1304) or chronic-untreated (CUN) stage infection (>6 months, n= 1809). Molecular recency assays based on sequence nucleotide ambiguity was nused to estimate recency of infection. Patterns of viral spread were stratified into four distinct groups based on cluster size (1, 2-4, 5-9, 10-91 infections/cluster). PHI cohort participant data ascertained partnership risk behaviour and viremia in four cluster groups. The SPOT rapid testing site cohort determined testing propensity and partnership risk among MSM.

Results: Over the last decade, MSM infections included 1168 solitude transmissions (37%), 244 small clusters (2-4 infections, n=573, 18%), 65 large clusters (5-9 infections, n= 403, 13%), and 45 large cluster (10-91, median 25 infections, n=969, 31%) network. The episodic genesis and spread of clusters was related to primary infection (27%, 46%, 50% and 54%, odds-ratio 1, 2.33, 2.81, 3.33, respectively). Viral lineages associated with unique, small, large (5-9) and (10-91) cluster groups showed significant differences in weighted sequence ambiguity (0.40%, 0.27%, 0.20%, 0.13%, respectively). PHI cohort data revealed extended viremia over 24 months in lineages associated with large cluster networks. The MSM epidemic is growing in younger populations, with 14%, 18%, 27%, and 32% of unique, small, large (5-9) and large (10+) below 30 years of age, respectively. PHI cohort data

show no significant differences in partnership risk behaviours in the four cluster groups. SPOT cohort data showed an inverse relationship between partnership risk behaviour and testing propensity.

Conclusions: The Montreal MSM epidemic is sustained by primary/recent stage infection with an ongoing genesis of large cluster viral lineages (median 16 infections/cluster) showing protracted infectivity. Overall 7% of lineages account for 70% of onward transmissions. These findings substantiate the need for frequent testing among increasingly younger and mixed risk MSM populations.

252 Sources of HIV-1 Transmission in the Ongoing, Concentrated HIV Epidemic Among Men Having Sex With Men in the Netherlands Between July 1996 and December 2010

Oliver Ratmann[1]; Ard van Sighem[2]; Daniela Bezemer[2]; Alexandra Gavryushkina[3]; Peter Reiss[2]; Frank de Wolf[1]; **Christophe Fraser**[1]

[1]Imperial College London, London, United Kingdom; [2]Stichting HIV Monitoring Foundation, Amsterdam, Netherlands; [3]University of Auckland, Auckland, New Zealand

Background: The HIV epidemic among men having sex with men (MSM) remains out of control. To better target HIV prevention efforts, it is critical to quantify the proportion of HIV transmissions that originate throughout the HIV treatment cascade, from undiagnosed to treated individuals.

Methods: We conducted a combined analysis using anonymized, molecular genetic and clinical data from HIV infected individuals in care in the Netherlands between 1996 and 2013. Patients were followed at high frequency in the open, national opt-out, clinical ATHENA cohort. Partial HIV-1 *pol* sequences were collected for 46% of all MSM in care. Using viral evolutionary analyses, we determined potential transmitters to 667 recipient MSM that were diagnosed with recent HIV infection up to December 2010. Using clinical data, we associated treatment cascade stages with potential transmission intervals.

Results: A total of 1,660 person-years of potential transmission intervals were associated with phylogenetic evidence for direct HIV-1 transmission. Overall, the estimated proportion of transmissions from undiagnosed individuals decreased from 66% (95% confidence interval: 52-79%) from May 2006 to December 2007 to 58% (43%-74%) from July 2009 to December 2010, while the estimated proportion of transmissions from individuals after ART initiation increased from 8% (4-12%) to 17% (12-22%) in the same observation periods. Considering the most recent period July 2009 to December 2010, 15% (10-20%) of all transmissions are estimated to originate from undiagnosed individuals with recent HIV infection at diagnosis, 24% (19-29%) from those undiagnosed with chronic HIV infection at diagnosis, 19% (14-25%) from those undiagnosed with no data on recency of HIV infection, 4% (2-5%) from diagnosed, recently infected individuals within the first 3 months after diagnosis, 6% (4-8%) from diagnosed untreated individuals with CD4 count >500, 15% (12-19%) from diagnosed, untreated individuals with CD4 count <500, and 10% (7-12%) from treated individuals with a viral load above 50 copies/ml plasma blood.

Conclusions: Due to its national opt-out policy, the open, clinical ATHENA cohort enabled the worldwide largest analysis to date into the sources of HIV infection amongst MSM. A combined approach appears to be required to bring this HIV epidemic under control, including expanded testing, universal ART coverage, and frequent monitoring of the treated population.

253 A Direct Comparison of Two Densely Sampled Western European HIV Epidemics: The UK and Switzerland

Manon L. Ragonnet-Cronin[1]; Mohaned Shilaih[2]; Huldrych F. Günthard[2]; Jurg Boni[2]; Sabine Yerly[3]; Valerie Delpech[4]; David Dunn[5]; Roger Kouyos[2]; Andrew J. Leigh Brown[1]
Swiss HIV Cohort Study/UK HIV Drug Resistance Database

[1]University of Edinburgh, Edinburgh, United Kingdom; [2]University Hospital Zurich, Zurich, Switzerland; [3]University Hospital Geneva, Geneva, Switzerland; [4]Public Health England, London, United Kingdom; [5]MRC CTU at UCL, London, United Kingdom

Background: The UK and Swiss (CH) HIV epidemics have both historically been driven by transmission of subtype B among men who have sex with men (MSM). The CH population is 1/8 the size of the UK and HIV prevalence in CH is nearly double that of the UK. Both epidemics are densely sampled, by the UK HIV Drug Resistance Database and the Swiss HIV Cohort Study respectively. Previous independent analyses have suggested dramatically different epidemic dynamics.

Methods: A bioinformatics pipeline to compare HIV transmission patterns was developed which included: maximum likelihood phylogenetic trees for subtype A1, B and C *pol* sequences against a background of global sequences; cluster detection at a range of bootstrap (70%-95%) and genetic distance (1.5% and 4.5%) thresholds; analysis of degree distributions by risk group and characterisation of HIV import for each country independently. We use univariate and multivariate logistic regression to predict cluster membership based on country, sampling date, risk group, ethnicity and sex.

Results: We analysed >8000 subtype B sequences from CH and >25000 from the UK. A genetic distance of 1.5% yielded mainly pairs in both. Clustering was much higher among UK sequences at all thresholds (35% vs 15% on average, $p<10^{-91}$) suggesting that the UK database is more likely to capture transmitting partners. The number of links for each clustered sequence (degree distribution) followed a power law in both, but shifted downwards for CH relative to the UK. Down sampling the UK dataset to match the size of the CH dataset revealed a more similar degree distribution ($p<10^{-5}$ vs $p<10^{-12}$), remaining higher for the UK in MSM ($p<10^{-8}$), but not for heterosexuals ($p=0.2$). Adjusting for sampling time in the logistic regression models reduced the clustering odds-ratio between countries from 3.1 to 2.2. Both countries showed extensive intermixing with other European countries (80% of direct links for CH and 60% for UK), and the UK also displayed linkage with other Anglophone countries (Australia, Canada and USA, 26% of links). Within Europe, Spain was the most frequently linked country (12% and 15% of all links for the UK and CH, respectively).

Conclusions: In conclusion, epidemic size, insularity and sampling time play a part in explaining the differences in clustering patterns between the CH and UK epidemics. Reduced clustering in CH is most significant among MSM, who seem more likely to have acquired the virus outside the country.

THURSDAY, FEBRUARY 26, 2015

Session P-B5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Next Generation of Next-Generation Sequencing

254 Present Applications of a High-Throughput, Single Measure HIV Genomic Incidence Assay

Sung Yong Park[1]; Tanzy Love[2]; Nolan Goeken[1]; Robert Bolan[3]; Alan S Perelson[4]; Michael Dube[1]; **Ha Youn Lee**[1]

[1]Keck School of Medicine at University of Southern California, Los Angeles, CA, US; [2]University of Rochester School of Medicine and Dentistry, Rochester, CA, US; [3]Los Angeles Gay and Lesbian Center, Los Angeles, CA, US; [4]Los Alamos National Laboratory, Los Alamos, CA, US

Background: Annual HIV incidence is the primary assessor for monitoring the epidemic's rise and decline. In pursuit of an accurate assay, we have proposed a genomic incidence assay utilizing fingerprints harbored in the HIV sequence population, which showed over 95% accuracy among 182 incident and 43 chronic samples. Still, two major hurdles must

be overcome before routine use in cross-sectional settings: 1) streamlining the cost and workflow, 2) ensuring proper classification between multiple-founder recent infections and chronic infections.

Methods: For enhancing the cost efficiency of the sequence-based assay, we developed a high-throughput next-generation sequencing platform; a signal-masking bioinformatics pipeline was devised to analyze 18,434 envelope gene segments (HXB2 7212-7601) obtained from 12 incident and 24 chronic patients. To give the assay power to appropriately discriminate multiple-founder recent infections from chronic infections, we formulated a mathematical model which posits the intersequence nucleotide base difference distribution of each subject's sequence sample as a function of infection duration and the number of founder sequences. This model was tested by analyzing HIV subtype B and C samples from 40 incident subjects with multiple founder viruses.

Results: First, the cost-effective pyrosequencing platform correctly classified all 12 incident subjects (100% sensitivity) and 23 out of 24 chronic subjects (96% specificity). Our signal-masking bioinformatics pipeline yielded a process error rate of 5.8×10^{-4} per base. Sampling simulations showed that the biomarkers were tolerant of the two factors most likely to affect the accuracy: sequencing errors and template resampling. Second, a quantitative guideline for segregating viral lineages was provided by our mathematical model, enabling us to assess when each subject was infected. The infection periods obtained from our model estimates and from Fiebig laboratory staging showed a statistically significant linear relationship ($p<0.0005$), correctly identifying all 40 individuals with incident infections.

Conclusions: The high-throughput platform permits the assay to be cost-effective, and when it is combined with our mathematical model, we can obtain recency signatures from the complex gene pool that arises from multiple founder viruses. Our sequence-based approach marks significant progress towards accurate determination of HIV incidence from genomic readouts measured from cross-sectional samples from a single blood draw.

255 A Comprehensive Analysis of Primer IDs to Study Heterogenous HIV-1 Populations

David Seifert[1]; Armin Töpfer[1]; Francesca Di Giallonardo[2]; Stefan Schmutz[2]; Huldrych F. Günthard[2]; Volker Roth[3]; Niko Beerenwinkel[1]; Karin J. Metzner[2]
[1]ETH Zurich, Basel, Switzerland; [2]University Hospital Zurich, Zurich, Switzerland; [3]University of Basel, Basel, Switzerland

Background: Haplotyping of HIV-1 populations is an essential step to better understand the evolutionary dynamics of the virus. With the advent of next-generation sequencing (NGS), haplotyping of viral populations has become feasible. Since HIV-1 is highly heterogeneous, several statistical methods have been devised to deal with error-prone NGS data, however, they often do not capture the population correctly. In order to correct for errors, the use of PrimerIDs (primer identifiers) has been proposed. Here, we used PrimerIDs to systematically estimate different enzymatic error rates and to comprehensively study the feasibility of PrimerIDs.

Methods: Plasmids containing full-length genomes of 5 HIV-1 clones were separately amplified in bacteria and then transfected into 293T cells. Generated infectious HIV-1 particles were pooled, DNase treated, and a fragment of the *pol* gene was reverse transcribed with SuperScript III reverse transcriptase (RT) and primers containing random 10-mers. Reverse transcription was performed in six independent replicates. Subsequently, nested PCR was performed using Platinum Taq DNA Polymerase followed by adapter ligation and sequencing with Illumina MiSeq.

Results: From an average number of 1.1 million reads, we called consensus sequences for PrimerIDs, each supported by at least 10 sequencing reads, to yield on average 11,000 consensus sequences per replicate. From these consensus sequences, we could call all mutant bases from the five reference viruses. We estimated a RT error rate of 6.23e-4 (95% CI: [6.13e-4, 6.32e-4]). We inferred the recombination rate of the RT to be 3.44e-5 (95% CI: [2.26e-5, 4.92e-5]). The PCR substitution rate of 1.18e-4 (95% CI: [1.14e-4, 1.22e-4]) was determined from those mutants having arisen in the first cycle of the PCR. We calculated the total number of transcribed RNAs to be on the order of 60,000 from the observed collision rate of 2%. We observed no sequence-specific bias in PrimerID frequencies, the same RT efficiencies as compared to commonly used short, specific RT primers, and no effects of primerIDs on the estimated distribution of the five viruses in the mix.

Conclusions: PrimerIDs allow for determining error rates in RT-PCR-NGS protocols and are applicable to study HIV-1 heterogeneity when attention is paid to collision rates. Given these advantages, the protocol is still labor- and cost-intensive and does not significantly improve on the variance of frequency estimates.

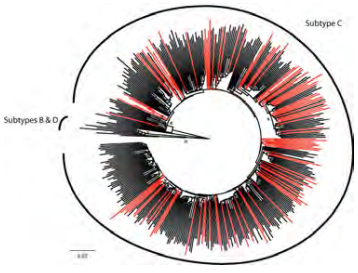
256 Near Full Length HIV-1 Sequencing to Understand HIV Phylodynamics in Africa in Real Time

Siva Danaviah; Justen Manasa; Eduan Wilkinson; Sureshnee Pillay; Zandile Sibisi; Sthembiso Msweli; Deenan Pillay; **Tulio de Oliveira**
University of KwaZulu-Natal, Durban, South Africa

Background: HIV transmission continues in Africa at alarming rates despite biological and behavioural interventions. Understanding the drivers of HIV transmission and evolution and translating the results into effective interventions is a key component of halting the epidemic. Recent technological advancement in complete genome sequencing has expanded the breadth and speed of genomic analyses currently possible. We have constructed a high-throughput genomics and bioinformatics pipeline that has successfully generated high quality complete HIV genomes in a hyper-endemic region of South Africa (SA), through the PANGEA_HIV Consortium

Methods: HIV RNA was extracted from plasma from patients failing antiretroviral therapy, within the Africa Centre (AC) research area and 4 overlapping regions spanning the 9.7kb complete HIV genome were amplified in a one-step RT-PCR strategy optimised for subtype C virus. Pooled amplicons were sequenced on an Illumina MiSeq. Fragments were quality controlled with SMALT software and assembled using two independent strategies (de novo and mapping to reference) in Geneious. Resulting consensus sequences were aligned against published HIV complete genomes from South Africa (n=300). Bayesian and maximum likelihood trees with branch support were reconstructed in PhyML and MrBayes.

Results: Amplification success rate of complete genomes, on samples with viral loads >10,000 c/ml was 85%. Near complete HIV genomes were generated for 117/117 samples sequenced thus far, with all nine open reading frames, the U5 / partial R region of the 5' LTR and partial U3 of the 3' LTR represented. Coverage of the HIV genome averaged 99.9% with a mean depth of coverage of 15 539 times (range = 21-48 767 times). Phylogenetic reconstruction confirmed that the AC strains were all HIV-1 subtype C where 36/117 sequences clustered with other complete genomes from SA. The discrete AC clusters (n=22) suggested multiple independent introductions of subtype C into the surveillance area and onward transmission within the population.



Maximum likelihood tree of 117 Africa Centre near full length HIV-1 complete genomes and 300 HIV-1 C genomes from South Africa. The tree is rooted on reference strains of subtypes B & D, branch support (bootstrap > 90) are marked with an *.

Conclusions: This is the first report, to the best of our knowledge, of a high-throughput complete HIV genome sequencing and analysis pipeline in Africa. The genetic diversity of HIV variants in this population is high and is mediated primarily by multiple introductions of HIV. Interventions therefore must be cognizant of the dynamics that drive these independent introductions in order to impact on going HIV transmission.

257 Pan-HIV Next-Gen Sequencing Strategy for Viral Surveillance

Michael G. Berg[1]; Julie Yamaguchi[1]; Elodie Alessandri-Gradt[2]; Jean-Christophe Plantier[2]; Catherine Brennan[1]

[1]Abbott Laboratories, Abbott Park, IL, US; [2]Virology Unit, National Reference for HIV, Rouen, France

Background: The complexity of HIV strains has increased significantly due to natural evolution and inter-subtype recombination; recombination is now a worldwide problem. Thus, complete genome sequencing is essential to monitor HIV diversity accurately within populations. Next-generation sequencing (NGS) has the potential to revolutionize strategies for HIV surveillance. We have developed a universal method that permits full genome sequencing of all HIV-1 groups (M, N, O, and P) and HIV-2.

Methods: Reverse transcription primers, designed in conserved regions of HIV and spaced at 1.5-2kb intervals, fuse viral sequences to a common adaptor (SMART) sequence. This same adaptor is added to the 3' end of the cDNA to permit PCR amplification of libraries, which are then tagmented with Nextera XT for multiplexing and sequencing on an Illumina MiSeq. HIV sequences are extracted and assembled in CLC-Bio software (Qiagen) and classified by phylogenetic analysis using PHYLIP and SIMPLOT.

Results: Broad application of the approach was demonstrated using a panel of virus isolates (n=47) derived from cell culture that included 27 group M (different subtypes and CRFs), 16 O, 2 N, 1 P, and 1 HIV-2. In a single run multiplexing 23 libraries, 100% genome coverage was obtained for each at a median depth of 2100X, with HIV reads comprising 9.4% (median) of the total. A Cameroonian HIV-1 non-subtype B specimen was used to optimize the protocol for plasma. An NGS run of 8 high titer ($>5.0_{log}$ copies/ml) clinical specimens, infected with diverse group M subtypes, yielded 96-100% coverage for each at a median 433X depth. Method sensitivity, demonstrated by serial dilution, showed that >50% of a genome could be obtained from a clinical specimen with a viral load $\geq 3.8_{log}$ copies/ml (100 RNA copies input). Due to inherent variability in sample background, coverage varied widely among specimens with viral loads $<4.5_{log}$. Nevertheless, sufficient sequence was obtained for strain classification. From the 55 novel full-length HIV sequences determined in this study, 5 are unique recombinants.

Conclusions: The HIV-SMART approach harnesses the specificity of HIV-directed priming without *a priori* knowledge of the viral strain present. This technology provides an unparalleled opportunity to identify diverse HIV strains in patient specimens and to determine phylogenetic classification based on the entire viral genome, illustrating the utility of NGS for viral surveillance.

258 PCR-Free Full Genome Characterization of Diverse HIV-1 Strains by Nextgen Sequencing

Viswanath Ragupathy[1]; Feng Gao[2]; Ana Sanchez[2]; Marco Schito[3]; Thomas Denny[2]; Michael Busch[4]; Jiangqin Zhao[1]; Christelle Mbondji[1]; SaiVikram Vemula[1]; Indira Hewlett[1]

[1]US Food and Drug Administration, Silver Spring, MD, US; [2]Duke Human Vaccine Institute and Departments of Medicine, Duke University Medical Center, Durham, NC, US; [3]Henry Jackson Foundation, DAIDS, NIAID, Bethesda, MD, US; [4]Blood Systems Research Institute/University of California San Francisco, San Francisco, CA, US

Background: HIV-1 genotyping is an important tool for clinical and epidemiological studies. High level of genetic variation, recombination and mutations pose difficulty in successful PCR amplification of HIV-1 genomes. In addition, new emerging subtypes may not be detected with standard PCR primers. Here, we report a novel PCR-free multiplex method for characterization of full length HIV-1 genomes (~9.7kb) using the Nextgen RNA Seq approach.

Methods: A total of 27 diverse HIV-1 strains representing subtypes A-G, CRFs, URFs and Group O were obtained from the Global HIV-1 diversity panel that was assembled at the Duke EQAPOL. Viral RNA was extracted, reverse transcribed as described in the Illumina Truseq RNA Kit and sequenced using the MiSeq platform. Sequence reads were quality filtered and reference mapped using CLC genomic work bench software v6.0.4. Consensus sequences were generated for each virus and used for phylogenetic tree analysis using the neighbor-joining method based on the Kimura two-parameter substitution model and recombination patterns were determined using Simplot. Drug resistance was inferred from the Stanford HIV drug resistance program, and co-receptor usage was determined using the Geno2Pheno (g2p) 5-10% FPR.

Results: The multiplex RNA sequencing approach yielded >10000x coverage for each of the viral genomes. Pools of viral isolates were de-multiplexed and discriminated using bio-informatics. After filtering reads specific for HIV-1, each position in the viral genome had >1000x coverage. This approach enabled reconstruction of whole genome HIV-1 haplotypes accurately including flanking LTRs. Analysis of full HIV-1 genome sequences using Simplot correctly identified 15 pure subtypes, one Group O virus, and recombination patterns of 8 CRFs and 3 URFs. All these HIV subtypes identified were comparable to Sanger sequencing. In addition, this approach revealed NNRTI, integrase and protease drug-specific minor variants and drug resistance mutations with >1000x coverage. The g2p analysis predicted 89% of isolates as being R5 tropic, and the remaining were identified as X4 tropic.

Conclusions: We have developed a reliable, PCR-free and multiplexing approach to characterize whole HIV-1 genome sequences. This novel PCR-free method can be used for characterization of new, emerging unknown subtypes or recombinants and to reduce PCR-derived sequence errors. The multiplexing approach makes this NGS method more cost-effective and less labor-intensive than conventional methods.

259 Full-Length Env Deep Sequencing in a Donor With Broadly Neutralizing V1/V2 Antibodies

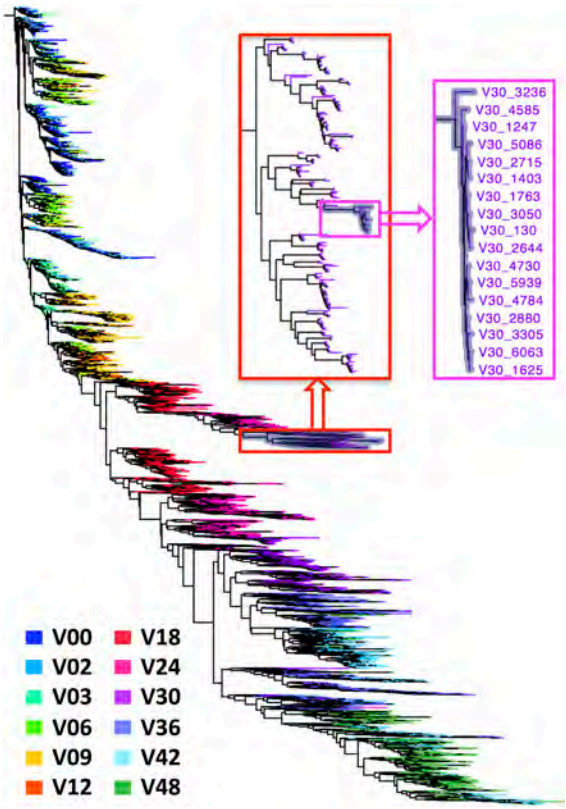
Ben Murrell[1]; Melissa Laird[2]; Elise Landais[3]; Caroline Ignacio[1]; Ellen Paxinos[2]; Pham Phung[4]; Sergei L. Kosakovsky Pond[1]; Douglas D. Richman[1]; Pascal Poignard[3]; Davey M. Smith[1]

[1]University of California San Diego, La Jolla, CA, US; [2]Pacific Biosciences, Menlo Park, CA, US; [3]The International AIDS Vaccine Initiative Neutralizing Antibody Center, La Jolla, CA, US; [4]LabCorp, South San Francisco, CA, US

Background: Understanding the co-evolution of HIV populations and broadly neutralizing antibody (bNAb) lineages may inform vaccine design. Novel long-read, next-generation sequencing methods allow, for the first time, full-length deep sequencing of HIV *env* populations.

Methods: We longitudinally examined *env* populations (12 time points) in a subtype A infected individual from the IAVI primary infection cohort (Protocol C) who developed bNAbs (62% ID50>50 on a diverse panel of 105 viruses) targeting the V1/V2 region. We developed a Pacific Biosciences single molecule, real-time sequencing protocol to deeply sequence full-length *env* from HIV RNA. Bioinformatics tools were developed to align *env* sequences, infer phylogenies, and interrogate escape dynamics of key residues and glycosylation sites. PacBio *env* sequences were compared to *env* sequences generated through amplification and cloning. *Env* dynamics were interpreted in the context of the development of a V1/V2-targeting bNAb lineage isolated from the donor.

Results: We collected a median of 6799 high quality full-length *env* sequences per timepoint (median per-base accuracy of 99.7%). A phylogeny inferred with PacBio and 100 cloned *env* sequences (10 time points) found cloned *env* sequences evenly distributed among PacBio sequences. Phylogenetic analyses also revealed a potential transient intra-clade superinfection visible as a minority variant (~5%) at 9 months post-infection (MPI), and peaking in prevalence at 12MPI (~64%), just preceding the development of heterologous neutralization. Viral escape from the bNAb lineage was evident at V2 positions 160, 166, 167, 169 and 181 (HxB2 numbering), exhibiting several distinct escape pathways by 40MPI.



Maximum likelihood phylogeny of the primary infection clade, inferred from longitudinal full-length deep sequenced HIV *env*. Terminal branches are colored by sample date (numbers in legend represent months post infection). Inset boxes show successively expanded phylogenetic detail, highlighting the sequencing depth. Very short terminal branches suggest low sequencing error rates.

Conclusions: Our PacBio full-length *env* sequencing method allowed unprecedented characterization of *env* dynamics and revealed an intra-clade superinfection that was not detected through conventional methods. The importance of superinfection in the development of this donor's V1/V2-directed bNAb lineage is under investigation. Longitudinal full-length *env* deep sequencing allows accurate phylogenetic inference, provides a detailed picture of escape dynamics in epitope regions, and can identify minority variants, all of which may prove useful for understanding how *env* evolution can drive the development of antibody breadth.

TUESDAY, FEBRUARY 24, 2015

Session P-C1 Poster Session
Poster Hall
2:30 pm – 4:00 pm

The Gut Microbiome

260 Functional Profiling of the Gut Microbiome in HIV Infection

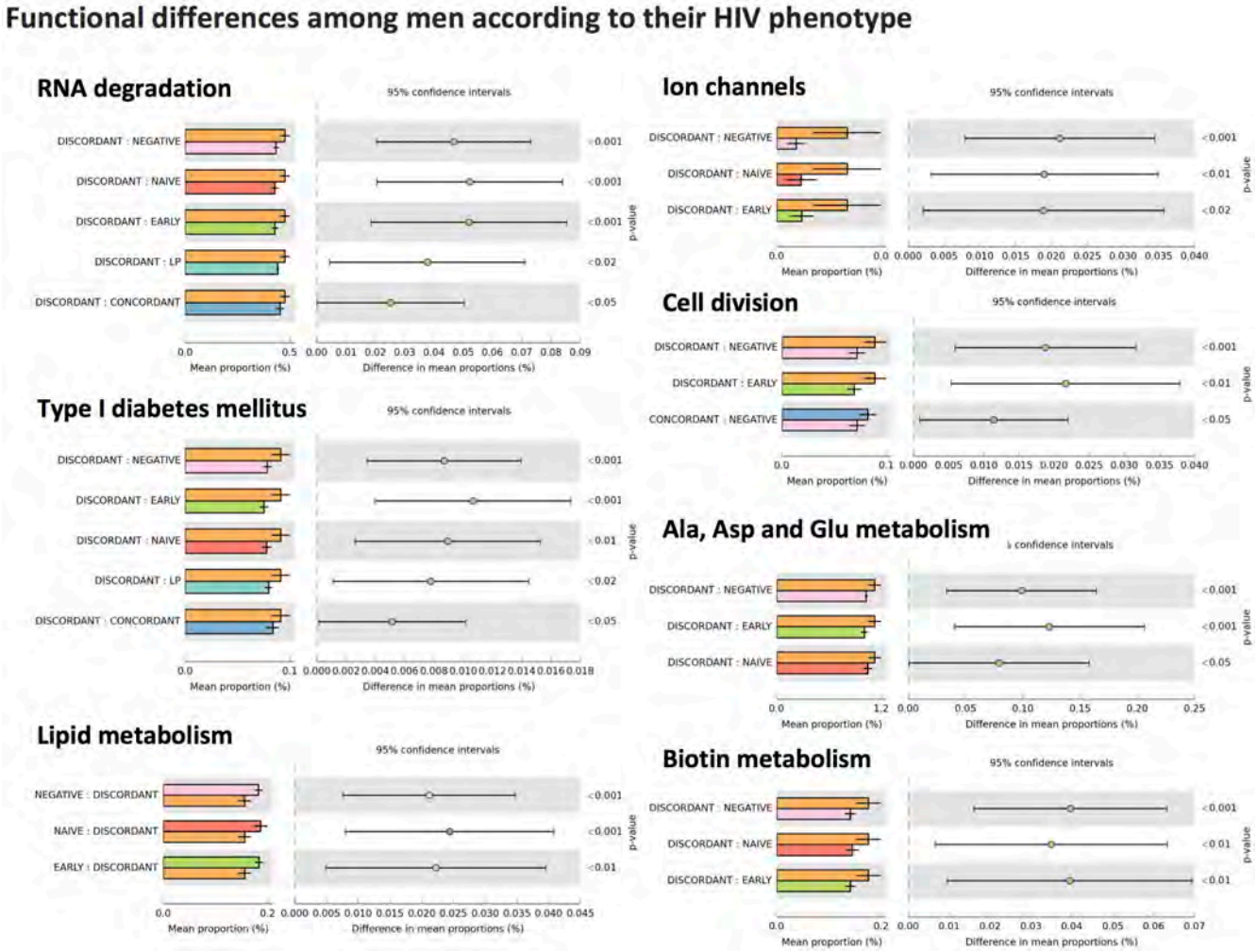
Yolanda Guillén; Marc Noguera-Julian; Muntsa Rocafort; Mariona Parera; Maria Casadellà; Isabel Bravo; Josep Coll; Julià Blanco; Bonaventura Clotet; Roger Paredes
MetaHIV Study Group

IrsiCaixa AIDS Res Inst, Hosp Univ Germans Trias i Pujol, Univ Autònoma de Barcelona, Badalona, Spain

Background: The gut microbiome plays an essential role in human physiology. We investigated to what extent HIV infection could modify its functions.

Methods: We used PICRUSt to infer the functional profile from 16S rRNA Miseq™ data, which was obtained in a cross-sectional study comparing the intestinal microbiome of HIV-negative (HIVneg) and HIV-1-infected subjects with different phenotypes, i.e., late presenters (LP: no ART, CD4≤200 c/mm^3), elite controllers (EC: no ART, HIV-1 RNA (VL)<50 c/mL for 1 year), viremic controllers (VC: no ART, VL 50-2000 c/mL for 1 year), ART-naïve (AN: no ART, CD4≥500 c/mm^3, VL>2000 c/mL), early treated (ET: ART started ≤6 months from HIV-1 infection, VL<50 c/mL), immune concordant (IC: on ART≥2 years, CD4≥500 c/mm^3, VL<50c/mL), and immune discordant (ID: on ART≥2 years, CD4≤300 c/mm^3, VL<50c/mL). Comparisons involving >2 groups were done using ANOVA plus Benjamini-Hochberg correction and Tukey-Kramer post-hoc tests; 2-group comparisons were performed with the Welch's t-test (STAMP package).

Results: The parent study included 80 subjects: 58 men, 21 women and 1 transgender woman. Relative to men, women showed significant enrichment in amino acid and carbohydrate metabolism, and in functions related to nervous and excretory systems. Within men, HIV+ subjects (5 LP, 1 EC, 3 VC, 6 AN, 5 ET, 17 IC, 8 ID) showed enrichment in functions related to membrane transport; Ala, Asp and Glu metabolism, and primary and secondary bile acid biosynthesis, as well as decreased lipid metabolism, relative to HIVneg (n=13). Most differences among HIV+ men involved the ID group (Figure), whose microbiome was enriched for genes related to RNA degradation; type I diabetes mellitus; ion channels; cell division; Ala, Asp and Glu metabolism, and biotin metabolism, and depleted in lipid metabolism. In addition, the microbiome of MSM (n=46) was enriched for carbohydrate and aminoacid metabolism, nervous and immune system functions, and depleted in biosynthesis of secondary metabolites, relative to MSW (n=9) and PWID (n=3) men. No differences were found by current or nadir CD4+ counts. Contrasting with previous reports, we found no differences in the tryptophan pathway in any of the former comparisons.



Conclusions: HIV infection, but also gender and sexual behavior influence gut microbiome functions. In particular, HIV infection is associated with bidirectional unbalances in intestinal metabolic activity, which do not seem to involve the tryptophan pathway.

261 Gut Microbiota Correlates with HIV-1 Control and Immune Status

Muntsa Rocafort; Marc Noguera-Julian; Yolanda Guillén; Mariona Parera; Maria Casadellà; Isabel Bravo; Josep Coll; Julià Blanco; Bonaventura Clotet; Roger Paredes
MetaHIV-Pheno Study Group
IrsiCaixa AIDS Res Inst, Hosp Univ Germans Trias i Pujol, Univ Autònoma de Barcelona, Badalona, Spain

Background: Recent studies suggest a role of the gut microbiome on HIV/AIDS pathogenesis, but it is unknown if the gut microbiota differs by HIV-1 control and immune status, or if antiretroviral treatment (ART) affects the intestinal microbial content to any extent.

Methods: This cross-sectional study compared HIV-1-negative (HIVneg) subjects with HIV-1-infected individuals with the following phenotypes: late presenters (LP: no ART, CD4≤200 c/mm^3), elite controllers (EC: no ART, HIV-1 RNA (VL)<50 c/mL for 1 year), viremic controllers (VC: no ART, VL 50-2000 c/mL for 1 year), ART-naïve (AN: no ART, CD4≥500 c/mm^3, VL>2000 c/mL), early treated (ET: on ART started ≤6 months from HIV-1 infection, VL<50 c/mL), immune concordant (IC: on ART≥2 years, CD4≥500 c/mm^3, VL<50c/mL), and immune discordant (ID on ART≥2 years, CD4≤300 c/mm^3, VL<50c/mL). Participants were 18-60 years old, had body mass index 18.5-30 and, except for LP, had no antibiotic usage during the previous 3 months. The fecal microbiota was characterized by massive 16S rRNA sequencing (MiSeq™). Richness (Sobs, Chao1 and ACE estimators), diversity (Shannon and Simpson indexes) and microbial taxonomic analyses were performed using Mothur and R/Vegan software packages.

Results: The study included 80 individuals: 16 HIVneg and 64 HIV-1+ (5 LP, 3 EC, 6 VC, 7 AN, 5 ET, 27 IC, and 11 ID). Compared with HIVneg, the gut microbiome of HIV-1+ subjects had lower richness and diversity (Table). By HIV-1 phenotype, IC, ID, EC, VC and LP had less observed OTUs (S_{obs}) and lower Shannon diversity than HIVneg, although the latter comparison was not statistically significant for EC. At the phylum level and relative to HIVneg, there were significant decreases in Firmicutes in IC, ID and LP; reductions in Lentisphaerae in IC, ID and VC, and increases in Bacteroidetes in ID. Proteobacteria were reduced in EC and increased in ET. The Firmicutes family Ruminococcaceae decreased in ID and LP. Among the Bacteroidetes families, Bacteroidaceae increased in IC, ID and EC; Porphyromonadaceae increased in IC and ID and Prevotellaceae decreased in IC, ID and EC. Both ET and AN remained similar to HIVneg across comparisons.

	Richness			Diversity	
	Sobs	Chao1	ACE	Shannon	Simpson
HIVneg	431.5	1906.18	1645.54	4.18	0.94
All HIV+	328 ***	1749.07 *	1359.41 **	3.72 ***	0.93 *
LP	322 **	1771.11	1488.09	3.59 **	0.91
EC	275 **	1755.50	1084.09 **	3.41	0.93
VC	299.5 ***	1937.81	1469.57	3.29 **	0.93 **
AN	372	2636.79	1572.28	4.25	0.95
ET	414	1759.54	1409.11	4.53	0.97
IC	330 ***	1643.52 **	1316.28 **	3.92 **	0.94
ID	250 ***	1389.50 *	1205.35 ***	3.46 ***	0.90 **

Median values are shown. Uncorrected Wilcoxon p-values, relative to HIVneg: *p=0.05-0.1, **p=0.01-<0.05; ***p<0.01.

Conclusions: Bacterial gut microbiota composition differs by HIV-1 phenotype and is affected by ART and immune recovery. Initiation of ART while CD4+ remain >500 cells/mm^3 and, particularly, during the first 6 months following HIV-1 infection preserve the gut bacterial content.

262 Butyrate Reduces Pathobiont-Associated HIV-1 Infection and Activation of Gut T Cell

Jon Kibbie; Stephanie Dillon; Eric Lee; Charles Robertson; Daniel N. Frank; Martin McCarter; Cara C. Wilson
University of Colorado Anschutz Medical Campus, Aurora, CO, US

Background: We previously reported that untreated chronic HIV-1 infection is associated with an altered intestinal microbiome that was linked to mucosal and systemic inflammation. HIV-1-infected (HIV+) subjects had increased abundances of pathobionts (e.g. Prevotella) and decreased abundances of bacterial families that contain butyrate-producing bacterial species (BPB). Butyrate is a short chain fatty acid important in intestinal immune regulation. We hypothesized that butyrate would decrease pathobiont-driven mucosal inflammation and investigated this using an *ex vivo* intestinal cell model.

Methods: Species identification was performed on bacterial 16S ribosomal DNA sequences previously obtained from colon biopsies of 17 untreated chronic HIV+ and 14 uninfected (HIV-) subjects. For analysis, the percent abundances of known colonic BPB (n=15 species) were pooled for each subject. Lamina propria mononuclear cells (LPMC) from normal human intestinal tissue (n=7) were infected with HIV-1_{BaL} and cultured with *P. stercorea* and butyrate: 0mM, 0.2mM (low) or 2mM (physiologic). Measurements of CD4 T cell activation (CD38+HLA-DR+) and infection (intracellular Gag-p24; ip24) were performed by flow cytometry. Levels of T cell-associated cytokines IFNγ, IL-17 and IL-2 were measured by ELISA. t-tests were used for statistical analysis.

Results: Abundances of BPB were lower in HIV+ subjects compared to HIV- controls (p=0.009). In HIV-1_{BaL}-infected LPMC, without butyrate, *P. stercorea* increased T cell activation (p=0.005), induced IFNγ (p=0.005), IL-17 (p=0.001) and IL-2 (p=0.03) production and increased frequencies of ip24$^+$ CD4 T cells (p<0.0001). With 2mM butyrate, *P. stercorea*-associated T cell activation was decreased by 85% (p<0.05), production of IFNγ (p<0.01), IL-17 (p<0.01) and IL-2 completely abrogated, and T cell infection levels decreased 3-fold (p=0.01). Lower butyrate concentrations failed to inhibit *P. stercorea*-induced T cell activation and infection, induced a 2-fold decrease in IFNγ and IL-17 (p<0.05), but increased IL-2 production.

Conclusions: Untreated, chronic HIV+ subjects have decreased abundances of BPB in the colonic mucosa. In an *ex vivo* intestinal cell model, physiological levels of butyrate decreased T cell activation, cytokine production and HIV infection induced by *P. stercorea*, a pathobiont increased in the colonic mucosa of HIV+ subjects, whereas lower levels did not. These findings suggest that a loss of BPB in the gut microbiome may contribute to HIV-associated mucosal pathogenesis.

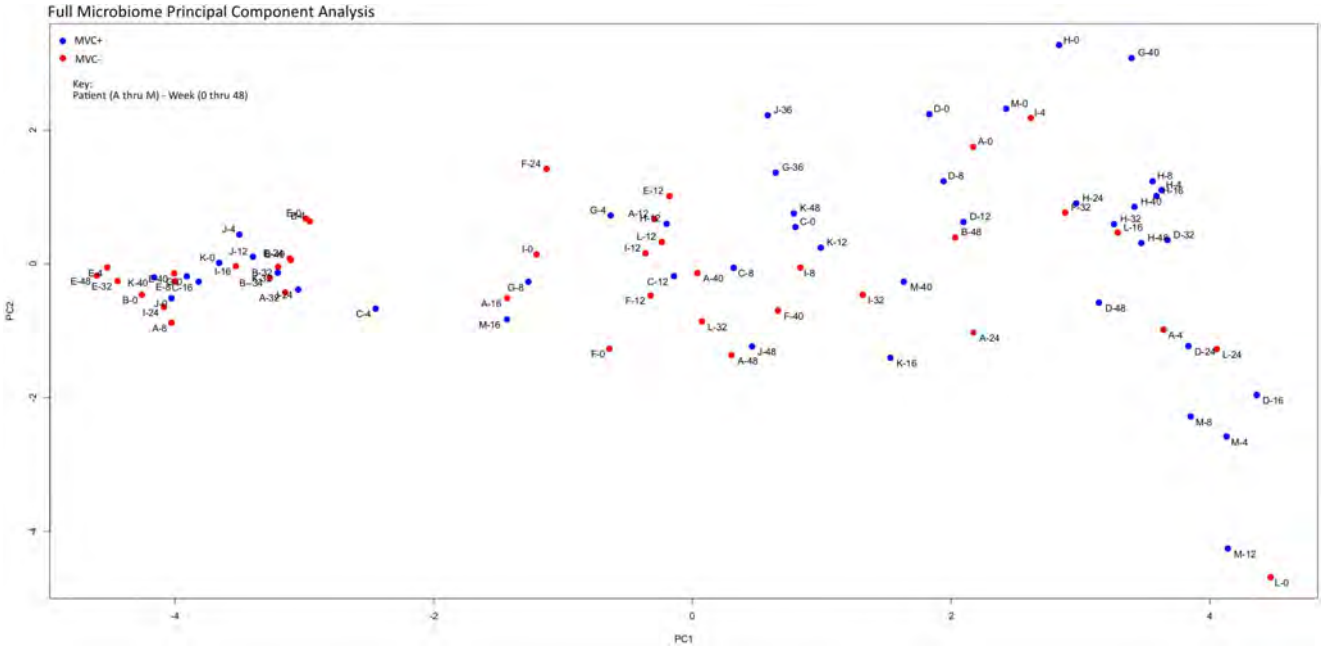
263 Maraviroc Does Not Induce Changes in the Gut Microbiome of HIV-Infected Individuals

Andrej Vitomirov; David M. Smith; Susanna R. Var; Maile Karris; Parris Jordan; Douglas D. Richman; Susan Little; Josué Pérez-Santiago
University of California San Diego, La Jolla, CA, US

Background: HIV preferentially depletes CD4 T cells in the gut-associated lymphoid tissue during acute infection, likely associated with high levels of CCR5 expression. Maraviroc (MVC) blocks HIV entry by binding CCR5. The consequences of MVC treatment on the gut microbiome have not been investigated. Here, we evaluated the impact of antiretroviral treatment (ART) plus MVC intensification on the gut microbiome during primary HIV infection.

Methods: Thirteen recently HIV infected persons in the San Diego Primary Infection Cohort were randomized to receive early ART (atazanvir, ritonavir, tenofovir and emcitritabine) with or without MVC. Anal swabs were collected prior to the start of ART and approximately every 4 weeks thereafter for 48 weeks. Stool DNA was extracted from the swabs and the V6 region of the 16s rDNA gene was pyrosequenced. We classified bacterial sequences at the order level and evaluated microbiome profile differences cross-sectionally and longitudinally between persons who did (MVC+) or did not (MVC-) receive MVC. All analyses were performed with R statistical software.

Results: We classified 13 orders of bacteria that were shared among all participants at baseline. We then compared each order of bacteria between MVC+ (n=6) and MVC- (n=7) individuals at weeks 4, 24, and 48 after initiation of ART. The distribution of bacterial orders between groups did not differ statistically (p>0.05) at any time point (Mann-Whitney test). In a paired analysis comparing baseline bacterial levels with weeks 4, 24, and 48 between MVC groups, we found no differences in the levels of each order of bacteria (Wilcoxon test); however, there was a trend for a reduction of the order of Actinomycetales from baseline to week 48 (p=0.06). When we evaluated the full microbiome of all participants at all time points measured using principal component analysis, there were no clusters based on MVC intensification (see figure).



Principal component analysis of the gut microbiome of patient samples obtained at each timepoint. Each dot, labeled with a letter followed by a number, corresponds to a single sample in which each letter (A through M) corresponds to a patient and the number (0 through 48) identifies at which week the sample was taken. Red points belong to the MVC- group and blue points belong to the MVC+ group. There is no evidence of clusting by MVC group.

Conclusions: In early HIV infection, CCR5 blockade with MVC may be a potent antiviral strategy for reducing the depletion of CD4 lymphocytes in the gut but, it does not significantly alter the gut microbiome. As such, Maraviroc may be a beneficial addition to treatment strategies involving reshaping the gut microbiome.

264 Fecal Microbiota of HIV Controllers Is Similar to That of Non–HIV-Infected Individuals

Selma N. Alva Hernández; Sandra M. Pinto Cardoso; Norma Téllez; Akio Murakami-Ogasawara; Gustavo Reyes-Terán

National Institute of Respiratory Diseases, Research Center in Infectious Diseases, Mexico City, Mexico

Background: Less than 5% of the HIV-infected population is able to control HIV infection in the absence of antiretroviral therapy (ART). This population is commonly defined as HIV controllers (HIC). Studying this population represents a unique opportunity to understand the mechanisms responsible for HIV control. The aim of this study was to address whether HIC have the same alterations in the composition of their gut microbiota as described in chronic HIV infected individuals naïve to ART (CI).

Methods: All participants gave written informed consent. DNA was extracted from stool samples collected from 20 CI, 6 HIC (as defined by viral loads below of 2,000 copies of RNA/mL) and 9 non-HIV-infected individuals (NI). The V3 region of the 16S rRNA gene was PCR amplified and sequenced using a semiconductor sequencer. After quality filtering, taxonomic assignment and alpha diversity (rarefied at 49,208 sequences/sample) were computed using QIIME 1.8.0. Comparisons between groups were performed using Mann-Whitney U-test and Kruskal-Wallis test (GraphPad Prism 5).

Results: Median CD4 counts were 436 cells/mm^3 (237-821) and 947 cells/mm^3 (482-1,160) for CI and HIC respectively; p=0.002. Median plasma viral loads were 74,408 copies of RNA/mL (3,462-2,030,199) and 62 copies of RNA/mL (<40-447) for CI and HIC respectively; p=0.0003. As previously reported, we found lower microbiota diversity in CI than in NI (1,195 ± SD 487 vs 1,652 ± 296, p=0.040). Interestingly, no differences in microbiota diversity were observed between HIC and NI (1,472 ± 655 vs 1,652 ± 296, p=0.689). We found three predominant phyla: *Bacteroidetes*, *Firmicutes* and *Proteobacteria* with an overall median relative abundance of 83.9% ± 17.7%, 11.9 ± 11.6% and 2.0% ± 11.0%, respectively. No significant overall differences were observed at phylum level (p=0.442, 0.479 and 0.555, respectively). However, at family level, we found a significantly lower abundance of both Ruminococcaceae and Lachnospiraceae in CI when compared to NI (p=0.028 and 0.008, respectively). At genus level, no significant differences were found between *Prevotella* and *Bacteroides*, the two most abundant genera belonging to the phylum *Bacteroidetes*, and reported altered in CI (p=0.335 and 0.536, respectively).

Conclusions: HIV controllers do not have significant alterations in gut microbiota composition, previously reported in chronic HIV infected individuals naïve to ART. The fecal microbiota of HIV controllers resembles that of non-HIV-infected individuals.

265 Impact of 2 Antiretroviral Regimens on Fecal Microbial Diversity and Composition

Sandra M. Pinto Cardoso; Selma N. Alva Hernández; Norma Téllez; Akio Murakami-Ogasawara; Gustavo Reyes-Terán

National Institute of Respiratory Diseases, Mexico City, Mexico

Background: Reports have shown that microbial composition of individuals on antiretroviral therapy (ART) is different from that of non-HIV-infected individuals. However, the degree to which ART restores the microbial composition remains unclear. The aim of this study was to determine the effect of two types of ART regimens: Efavirenz-based regimen (EFV) and protease inhibitor-based regimen (PI) boosted with either Lopinavir (LPV/r) or Atazanavir (ATV/r) on fecal microbial diversity and composition.

Methods: All individuals gave informed consent. Fecal samples were obtained from 37 HIV-infected individuals: 20 on EFV-based regimen and 17 on a PI-based regimen and 9 non-HIV-infected individuals. The V3 region of the 16S rRNA gene was PCR amplified and sequenced on a semiconductor sequencer. Alpha diversity computation (observed species rarified at 49,208 sequences/sample), operational taxonomic unit (OTU) picking at 97% ID and taxonomy assignment was performed using QIIME 1.8.0. Statistical analysis was performed using two-tailed Mann-Whitney U-test (GraphPad Prism 6).

Results: Median CD4 counts were 457 cells/mm3 (235-1247) and 559 cells/mm3 (240-1177) for individuals on EFV- and PI-based regimen respectively (p=0.174). All individuals on ART had undetectable viral loads. Median duration of ART was 70 months ± SD 33.36. Individuals under EFV- had significantly lower diversity compared to those on PI-based regimen (p=0.0304) and to non-HIV-infected controls (p=0.0030). Microbial communities were profiled and four predominant phyla were found: Bacteroidetes, Firmicutes, Proteobacteria and Fusobacteria. The phylum Fusobacteria was only observed in individuals under EFV-based regimen (overall RA= 3.591% ± SD 9.05%). The relative abundance

(RA) of Bacteroidetes was significantly reduced in individuals receiving EFV- as compared to those receiving PI-based regimen (p=0.0054) and to non-HIV-infected controls (p=0.0175). At the genus level, the RA of Prevotella was significantly reduced (p=0.0415) and the RA of Bacteroides was significantly enriched (p=0.0328) in individuals receiving EFV- compared to PI-based regimen.

Conclusions: Individuals on EFV-based regimen showed an alteration along the Prevotella/Bacteroides gradient, compared to those on a PI-based regimen. Further analyses are required to account for confounding factors. Deciphering the effects of different ARV regimens on gut microbiota composition is of great interest to develop therapies aimed at restoring the latter to a healthy state.

266 Targeting Gut Dysbiosis With Prebiotics and Glutamine in HIV-Infected Subjects

Sergio Serrano-Villar[1]; Jorge Vázquez-Castellanos[2]; Alejandro Vallejo[1]; Sara Ferrando-Martínez[4]; Talía Sainz[3]; Mar Vera[5]; Santiago Moreno[1]; Andrés Moya[2]; María José Gosalbes[2]; Vicente Estrada[6]

[1]University Hospital Ramón y Cajal, Madrid, Spain; [2]FISABIO-Salud Pública, Valencia, Spain; [3]University Hospital La Paz, Madrid, Spain; [4]University Hospital Virgen del Rocío, Sevilla, Spain; [5]Centro Sandoval, Madrid, Spain; [6]University Hospital Clínico San Carlos, Madrid, Spain

Background: Altered interplay between gut mucosa and dysbiotic microbes during treated HIV infection has been linked to chronic immune dysfunction. Studies evaluating the effects of therapies aimed at shaping gut microbiota in HIV-infected subjects are needed.

Methods: In this study, 45 subjects including 12 HIV+ viremic untreated (VU), 24 ART-treated virally suppressed (AT) and 9 HIV- controls (HIV$^-$) were blindly randomized to receive either prebiotics (scGOS/lcFOS) and glutamine or placebo (34/11), during 6 weeks. We performed a comprehensive assessment of changes in fecal microbiota composition using 16S rRNA deep sequencing and measured a number of immunological markers in plasma and PBMC.

Results: VU showed significantly higher bacterial richness (Chao1 and ACE estimators). In contrast, AT displayed the highest compositional heterogeneity (Shanon index). Unifrac distances showed that VU was the group with greatest bacterial dysbiosis, while AT represented an intermediate state between VU and HIV$^-$ (Adonis; all P<0.05). Using linear discriminant analylis effect size (LefSe) the most enriched bacteria in VU and AT patients was *Prevotella*, while *Bacteroides* and butyrate-producers bacteria were depleted.

Patients in the active arm experienced a compositional shift that was not appreciated in the placebo arm (Figure 1). Clustering analyses revealed that among VU and, to a lesser extent, among AT, the intervention shaped bacterial communities towards the HIV-uninfected group. LefSe indicated that in VU and AT *Prevotella* abundance decreased during the intervention. To identify potential microbial targets for interventions, we assessed in the active arm correlations between changes in dysbiotic bacteria and markers of disease progression. After adjusting for multiple comparisons, variations in *Butyrivibrio*, *Desulfovibrio* and *Blautia* strongly correlated with significant improvements of thymic output (sj/β TREC ratio), while changes in *Catenibacterium* and *Eubacterium* strongly correlated with significant declines of activated (%HLA-DR+CD38+) T cells in both VU and AT (all, P<0.05).

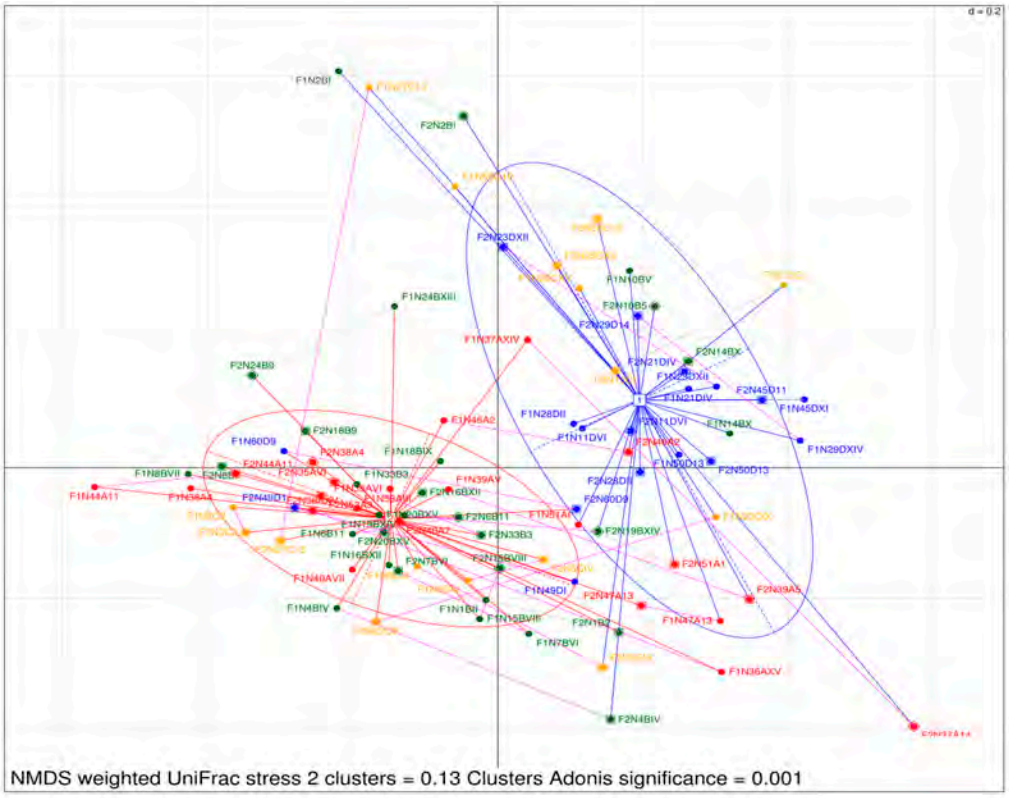


Figure 1. Changes in gut microbiota composition during the intervention.
NMDS of the unifrac distance matrix of the OTU bacterial composition in VU (red dots), AT ≥350CD4/mm3 (green dots), AT <350CD4/mm3 (orange dots) and HIV- (blue dots). The centroids are represented by numbers (1 and 2), while ellipses represent 70% of the samples belonging to each condition. Each point is connected with a dash line to another dot corresponding to the sample at the end of follow/up, purple lines indicates those samples that differs significantly from each other environment. Dots framed by a rectangle represent individuals after treatment with prebiotics and glutamine, dots framed by a diamond represent individuals after treatment with placebo.

Conclusions: A short dietary supplementation with prebiotics and glutamine ameliorated HIV-associated dysbiosis in ART naïve and treated patients, although gut microbiota of treated patients was found more resilient. We identified several bacteria correlated with improvements of markers of immune reconstitution and T cell activation, and hence, potential targets for interventions.

TUESDAY, FEBRUARY 24, 2015

Session P-C2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

The Mucosa in HIV/SIV Pathogenesis

267 Impact of Mucosal Immunity and HIV Persistence on CD4/CD8 Ratio After ART Initiation

Sergio Serrano-Villar[1]; Talía Sainz[2]; Tae Wook-Chun[3]; Netanya S. Utay[5]; Zhong-Min Ma[4]; Basile Siewe[6]; Steven Deeks[7]; Richard Pollard[4]; Christopher Miller[4]; David Asmuth[4]

[1]University Hospital Ramón y Cajal, Madrid, Spain; [2]University Hospital La Paz, Madrid, Spain; [3]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US; [4]University of California Davis, Davis, CA, US; [5]University of Texas, Galveston, TX, US; [6]Rush University Medical Center, Chicago, IL, US; [7]University of California San Francisco, San Francisco, CA, US

Background: The CD4/CD8 ratio correlates with persistent T-cell dysfunction and mortality. We examined the impact of changes (Δ) in the HIV reservoir, systemic inflammation/bacterial translocation and mucosal immunity following ART initiation on CD4/CD8 ratio.

Methods: 33 ART naïve HIV subjects were randomized to efavirenz, maraviroc or maraviroc+raltegravir, each with tenofovir/emtricitabine. Colon and duodenal biopsies were obtained at baseline (BL) and after 9 months of suppressive ART. Duodenal CD4 T-cell density (cells/mm^2) was counted by immunofluorescence antibody (IFA) labeling. Tissue was digested into single-cell suspensions for immunophenotyping. Cell-associated HIV RNA and proviral DNA, lymphocyte subsets and activation phenotypes (CD38$^+$/HLA-DR$^+$) were measured in duodenum, and colon, and in peripheral blood (PB) at BL, month 3, 6, and 9. Plasma IL-6, lipoteichoic acid (LTA), sCD14 and zonulin were measured by ELISA. Associations between ΔCD4/CD8 ratio and variations of continuous variables were analyzed using linear mixed models with random intercepts.

Results: The CD4/CD8 ratio significantly improved during ART in all compartments but recovered less in duodenum (all P<0.001). No difference was observed between the regimens (P=0.102) (Figure 1). Higher PB ΔCD4/CD8 ratio was associated with greater decay of HIV-DNA and HIV-RNA. In PB these correlations were significant for both HIV-RNA and HIV-DNA levels (P<0.001), but only PB ΔCD4/CD8 increments predicted colonic RNA-HIV declines (P=0.001). Increases in CD4/CD8 ratio were related to increased zonulin levels (P=0.076).

Higher CD4/CD8 was consistently associated with a lower % of activated CD8 T-cells in PB (Rho -0.74, P<0.001) and colon (Rho -0.48, P=0.002). PB ΔCD4/CD8 increases predicted comparable declines of T-cell activation in PB and colon (P<0.001) and Δnaïve/memory increases in PB and colon (P<0.001), but not any of these phenotypes of CD4 T-cells in duodenum. A higher PB ΔCD4/CD8 ratio was associated with significant improvements of duodenal CD4-T cells/mm^2, which still remained profoundly impaired at the end of follow-up (mean CD4 cells/mm^2: at baseline, 48, at month 9, 151; in controls: 674; P<0.001).

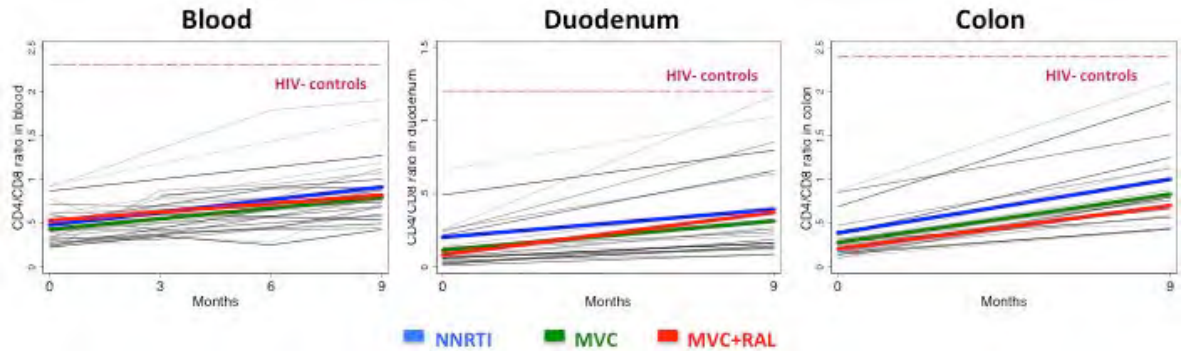


Figure 1. Changes in CD4/CD8 ratio in three compartments during first-line ART. Individual participant trajectories are represented by grey lines. Dash lines represent levels observed in HIV-uninfected individuals. Red, green and blue lines represent mean changes for each treatment arm predicted by linear mixed-effects models adjusted for baseline CD4 counts.

P values for the interaction between treatment arms and time did not reach statistical significance in any compartment.

Conclusions: CD4/CD8 recovery during ART correlates with improvements in markers of viral persistence, T cell activation and T cell maturation in PB and colon. The duodenum may represent a unique compartment for impairment of CD4 maturation and depletion. A quadruple ART regimen did not add detectable benefit to triple ART.

268 Monocyte/Macrophage Activation and Recruitment to Mucosal Sites in SIV Pathogenesis

Jan Kristoff[1]; Jenny Stock[1]; Tianyu He[1]; Bruno Andrade[2]; Benjamin Policicchio[1]; Alan Landay[3]; Ivo Francischetti[2]; Cristian Apetrei[1]; Irini Sereti[2]; **Ivona Pandrea**[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US; [3]Rush University, Chicago, IL, US

Background: Monocytes/macrophages (Mo/Ma) assume unique functions in HIV infection, being linked to microbial translocation, immune activation and inflammation (IA/INFL). We compared the fate of Mo/Ma in pathogenic, nonpathogenic and controlled SIVsab infection of pigtailed macaque (PTM), African green monkey (AGM) and rhesus macaques (RM) to better define their role in SIV pathogenesis.

Methods: We assessed Mo/Ma subsets (CD14, CD163, CD16), mobilization (CCR5, a4b7, CCR7, CXCR3), IA (CD80, 86, Ki-67, CCR5, TF), apoptosis (Cas-3), cytokine production (IL-6, IL-10, IL-12 and TNF-a), and phagocytic capacity of Mo/Ma in blood, LNs and intestine. We measured soluble Mo activation markers (sCD14, sCD163, sTF). Tissue infiltration of Ma was assessed by HAM56, CD68, CD163, CD16. Ma trafficking in tissues was assessed by administration of iron oxide microparticles.

Results: Increased CCR5 Mo expression correlated with their loss in circulation and increases in the gut in SV-infected PTMs. Increased CCR7 Mo expression was associated with Ma increase in the LNs in AGMs. No significant Mo/Ma variations were observed in RMs. Increased Mo/Ma proliferation occurred at all sites in PTMs, only in LNs in AGMs, and mainly in blood in RMs. Increased CCR5, CD80, CD86 and TF were observed on Mo/Ma from PTMs, while no changes occurred in AGMs. In RMs CD80 only increased in blood, while CD86 was decreased. Increased Mo/Ma apoptosis occurred early in PTMs and RMs, but was absent in AGMs. Phagocytic activity increased in PTMs but not in AGMs or RMs. Mo produced higher amounts of IL-6 and IL-12 in PTMs, IL-10 and 12 in RMs, while inflammatory cytokine did not increase in AGMs. In the gut AGM Ma produced IL-10, while PTM Ma produced IL-6 and TNF in addition to IL-10. RMs Ma did not show increases in cytokine production in the gut. Soluble markers of monocyte activation and sTF increased throughout infection in PTMs, but not AGMs. Massive infiltration with Ma was observed in LNs, gut, liver, lung and heart in chronically-infected PTMs but not in AGMs and RMs. Ma containing microparticles were found in liver, spleen, myocardium and pericardium in progressive hosts.

Conclusions: Progressive SIV infection is associated with increased activation, apoptosis and massive Mo recruitment to mucosal and nonmucosal tissues. These data suggest that Mo/Ma fuel immune activation and inflammation and development of comorbidities that distinguish progressive from nonprogressive SIV infection.

269 Rectal Tenofovir Gel Usage Is Associated With Changes in the Mucosal Proteome

Adam Burgener[1]; Laura Romas[1]; Kenzie Birse[1]; Kenneth H. Mayer[3]; Irma Febo[5]; Ross Cranston[2]; Alex Carbarballo-Dieguez[4]; Ian McGowan[2]

[1]University of Manitoba, Winipeg, Canada; [2]University of Pittsburgh, Pittsburgh, PA, US; [3]Harvard Medical School, Boston, MA, US; [4]Columbia University, New York, NY, US; [5]University of Puerto Rico, San Juan, US

Background: After the success of the CAPRISA-004 clinical trial showing efficacy of vaginally-applied tenofovir (TFV)-based gels at preventing HIV infection, rectal formulations are currently being explored as a prevention option. However, further research is needed to characterize the safety of rectal microbicide gels. Standard mucosal safety tests, such as inflammatory cytokine measurements, may miss important immunological or biological side effects. Advances in systems biology tools, such as mass spectrometry, allow the monitoring of hundreds of mucosal immune factors simultaneously. Here we performed a comprehensive proteomic analysis to explore the impact of tenofovir 1% gel when applied rectally in the Project GEL study (MTN).

Methods: Project GEL was a phase 1 randomized, double-blind, multi-site, placebo- controlled trial in which in which 24 participants were randomized 1:1 to receive rectal tenofovir 1% gel or (HEC) universal placebo gel. Study participants received one dose at first visit under observation, and then after a one-week recovery period, seven consecutive once-daily doses. Rectal mucosal swabs were collected on each visit. Mucosal samples were then analyzed by label-free tandem-mass spectrometry. Data was normalized and log transformed, followed by statistical analysis including paired (time-effects) and unpaired (across study arm) *t*-tests to identify differentially expressed proteins. Only high power (low technical variance) proteins were utilized in downstream analysis.

Results: Over 249 unique proteins were identified in rectal mucosal samples. Within the TFV-arm, 7% (17/249, $p<0.05$) and 10% of total proteins changed (25/249, $p<0.05$) after 1 and 8 daily applications of TFV-gel, respectively, compared to 3% (7/249, $p<0.05$) and 6% (16/249,$p<0.05$) in the HEC arm. Biofunctional analysis utilizing DAVID gene ontology toolset indicated the TFV arm differentially expressed proteins were strongly associated with epidermal development ($p=5.1E-9$) and structural activity functions ($p=1.5E-07$), whereas HEC arm had milder associations with cell activation ($p=4.3E-3$) after 7 days usage.

Conclusions: These preliminary studies suggest that rectal TFV-gel usage may be associated with mucosal proteome changes related to epidermal development. Further long-term studies are warranted for validation of these biomarkers including the impact of TFV-based rectal microbicide gels on the overall mucosal proteome.

270 Links Between Systemic and Mucosal Immunity in Treated HIV Infection

Talía Sainz[1]; Sergio Serrano-Villar[2]; Gregory Melcher[3]; Zhong-Min Ma[3]; Christopher Miller[3]; Netanya S. Utay[4]; Basile Siewe[5]; Paolo Troia-Cancio[3]; Elizabeth Sinclair[6]; David Asmuth[3]

[1]Hospital Universitario Gregorio Marañón, Madrid, Spain; [2]Hospital Ramon y Cajal, Madrid, Spain; [3]University of California Davis, Davis, CA, US; [4]University of Texas Medical Branch, Galveston, TX, US; [5]Rush University Medical Center, Chicago, IL, US; [6]University of California San Francisco (UCSF), San Francisco, CA, US

Background: Recent data suggest that biomarkers of gut epithelial barrier dysfunction, bacterial translocation and inflammation predict mortality and are possibly linked to altered gut immunity. A better understanding of the underlying mechanisms might help to design interventions targetting chronic inflammation.

Methods: We assessed biomarkers of inflammation (IL-6) and gut barrier (lipoteichoic acid [LTA], sCD14 and zonulin) in a clinical trial comparing three different ART initiation regimens on 33 ART naïve HIV+ subjects. Peripheral blood, rectal and duodenal biopsies were obtained at baseline and 9 months after randomization. Immunohistochemistry of biopsies was performed to determine CD4 T cells/mm^2. Tissue was digested into single-cell suspensions for immunophenotyping. Spearman's rank correlation coefficients were assessed at month 9 and associations between changes in continuous variables over time were analyzed using linear mixed models with random intercepts.

Results: In duodenum, T-cell density correlated with plasma markers of gut barrier integrity: for CD4 T-cells and zonulin, Rho 0.59, $P=0.002$; for CD8 T-cells and lipoteichoic acid, Rho 0.67, $P<0.001$.

From maturational subsets, we observed significant correlations between zonulin and naive (CCR7+CD45RA+) CD8-T cells in colon and duodenum (Rho -0.51, $P<0.01$ and Rho -0.58, $P<0.01$) as well as with EM (CCR7+CD45RA-) CD8-T cells in colon and duodenum (Rho -0.58, $P<0.01$ and Rho -0.44, $P<0.01$). The naive/memory CD8 T-cell ratio in colon and duodenum correlated with zonulin levels (Rho 0.52, $P<0.01$and Rho 0.54, $P<0.01$, respectively). Transitional memory (TM) (CCR7-CD45RA-CD27+CD28+) CD4 T cells correlated with IL-6 levels (Rho -0.51, $P<0.01$)

Linear mixed models identified variations of intestinal T cell phenotypes significantly associated with changes of systemic markers: in duodenum, CD4 and CD8-T cells/mm^2, CD8+EM T cells and naive/memory CD8-T cell ratio predicted changes in zonulin levels, while in colon changes of CD4+TM predicted decreases of IL-6.

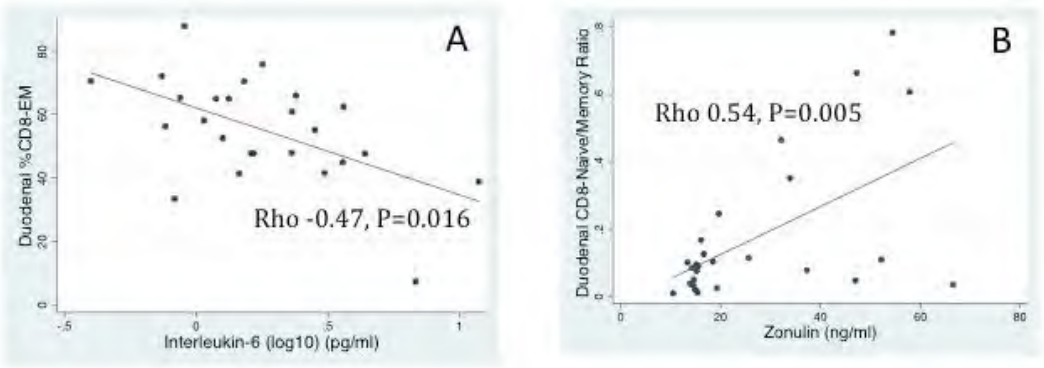


Figure 1. Correlations in treated HIV infected individuals between IL-6 levels and %CD8-Effector Memory cells in duodenum (A) and between zonulin levels and CD8-naive/memory T cell ratio in duodenum (B).

Conclusions: We observed a number of significant correlations between different intestinal T-cell phenotypes and systemic markers of inflammation and gut barrier integrity, suggesting that strategies aimed at modulating chronic inflammation may require targeting the gut immunity and/or gut microbial community composition.

271 No Impact of Early Intensified Antiretroviral Therapy on Gut Immune Reconstitution

Connie J. Kim[1]; Rodney Rousseau[2]; Colin Kovacs[3]; Sanja Huibner[2]; Gabor Kandel[4]; Erika Benko[3]; Kamnoosh Shahabi[2]; Tae Wook Chun[5]; Mario Ostrowski[2]; Rupert Kaul[2]

[1]Toronto General Hospital, Toronto, Canada; [2]University of Toronto, Toronto, Canada; [3]Maple Leaf Medical Clinic, Toronto, Canada; [4]St. Michael's Hospital, Toronto, Canada; [5]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

Background: HIV infection is characterized by reduced mucosal Th22 and Th17 cell numbers and function, which contribute to microbial translocation and inflammation. Standard antiretroviral therapy (ART) is slow to reverse these mucosal defects, and the resulting persistent inflammation is linked to serious non-AIDS illnesses (SNAs). We examined whether ART intensification with maraviroc and raltegravir during very early HIV infection would accelerate the resolution of gut immune dysfunction, microbial translocation, and SNA biomarkers.

Methods: ART-naïve men with early HIV infection were randomized 1:1 in a double-blind manner to receive standard ART (emtricitabine/tenofovir + lopinavir/ritonavir) with either raltegravir (400 mg/day) and maraviroc (150 mg/day), or placebo, for 48 weeks [NCT01154673]. In a predefined substudy, paired blood and sigmoid biopsies were collected from participants at baseline and week 48, and from HIV-uninfected controls. Mucosal CD4 T cell immunology (Th1, Th17 and Th22 cells), and blood markers of microbial translocation (LPS), immune activation (sCD14) and SNA (IL-6 and D-dimer) were assessed.

Results: Twenty-two participants documented to have acquired HIV a median of 4 months ago were enrolled. Prior to ART initiation, gut Th22 cell numbers ($P<0.001$) and Th17 polyfunctionality ($P=0.001$) were reduced compared to controls, and plasma LPS ($P=0.033$) and D-dimer levels ($P=0.020$) were elevated. At 48 weeks after ART initiation, overall gut Th22 cell numbers were restored ($P=1.00$), but plasma LPS levels ($P=0.226$) and gut Th17 function ($P=0.990$) were unchanged, and blood D-dimer levels had actually increased ($P=0.020$). ART intensification had no impact on gut CD4 T cell immune subsets (Th1, Th17 and Th22 cells), microbial translocation (LPS), or SNA biomarkers (D-dimer and IL-6); there was a trend to reduced plasma sCD14 in the intensified arm ($P=0.080$).

Conclusions: Early HIV infection was associated with substantial gut mucosal immune dysfunction, bacterial translocation and systemic inflammation. Regardless of intensification with raltegravir and maraviroc, one year of ART had a limited impact on mucosal immune reconstitution or blood markers of microbial translocation, inflammation, and SNAs.

272 Altered Properties of Mucosal NK Cell Subsets During Acute HIV-1 Infection

Alexandra Schuetz[1]; Yuwadee Phuang-Ngern[1]; Eugene Kroon[1]; Rungsun Rerknimitr[3]; Nitiya Chomchey[2]; Nittaya Phanuphak[2]; Merlin L. Robb[4]; Jerome H. Kim[4]; Mark de Souza[2]; Jintanat Ananworanich[4]
RV254/SEARCH 010 and RV304/SEARCH 013 Study Groups

[1]Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand; [2]Thai Red Cross AIDS Research Center, Bangkok, Thailand; [3]Chulalongkorn University, Bangkok, Thailand; [4]US Military HIV Research Program, Silver Spring, MD, US

Background: The role of mucosal innate immunity during acute HIV infection (AHI) is poorly understood, however increasing evidence supports a beneficial role of natural killer (NK) cells. Here, we investigate the distribution and activation of mucosal NK cell subsets during early AHI.

Methods: 27 subjects in Fiebig (F) I (n=11) and FIII (n=16) underwent sigmoid biopsy at the time of AHI diagnosis. Ten gender- and age-matched HIV-uninfected (HIV-) and 5 ART-naïve chronically HIV-infected (CHI) subjects served as controls. Mucosal mononuclear cells were isolated, and NK cell subsets were defined by the expression of $CD56^{(neg, dim, bright)}$ and NKp44 using multi-parameter flow cytometry.

Results: At the time of diagnosis, FI subjects had similar frequencies of total NK cells compared to HIV- and CHI, while FIII subjects showed a significant expansion (Table 1). In contrast surface expression of the activating natural cytotoxicity receptor, NKp44, was significantly increased on total NK cells at FI compared to FIII, HIV- and CHI. $CD56^{dim}$ cytolytic NK cells were the dominant subset of NK cells and were significantly decreased in FI and FIII patients compared to HIV- and CHI. The expression of NKp44 on $CD56^{dim}$ NK cells correlated inversely with plasma HIV RNA ($r=-0.48$, $p=0.01$). However, FI patients showed a significantly higher expression of NKp44 compared to FIII, HIV- and CHI. The frequency of immunoregulatory NK cells ($CD56^{bright}$) also decreased in FI and FIII compared to HIV-, and did not recover during CHI. In contrast, a significant expansion of the $CD56^{neg}$ NK cell subset, associated with chronic viral infection, was observed in FI and FIII compared to HIV- and CHI.

Table 1: Frequencies (%) of NK cell populations.

NK Cell Population	Fiebig I	Fiebig III	HIV-	CHI
total NK	20.3	28.5*	20.9	22.0
total NK NKp44+	9.9	4.4*	5.3*	6.3*
$CD56^{dim}$ NK	65.9	64.5	82.5***	87.1***
$CD56^{dim}$ NK NKp44+	12.1	4.9*	4.4***	2.1**
$CD56^{bright}$ NK	3.4	3.2	6.3*	2.7
$CD56^{neg}$ NK	24.6	26.7	8.9***	8.2***

All data are median (interquartile rang); All comparisons were made to Fiebig I: *p≤0.05, **p≤0.01 and ***p≤0.001

Conclusions: Distribution of mucosal NK cells subsets is altered during early AHI characterized by the loss of cytolytic $CD56^{dim}$ and immunoregulatory $CD56^{bright}$ NK cells and the expansion of $CD56^{neg}$ NK cells, a dysfunctional subset associated with impaired cytotoxicity. The reason for the early loss, without recovery, during CHI of the $CD56^{bright}$ subset warrants further investigation in the pathogenesis of HIV infection.

273 Loss of Cervical Gamma Delta 1 T cells in HIV-Infected Women

Natasa Strbo[1]; Maria L. Alcaide[1]; Laura Romero[1]; Hector Bolivar[1]; Deborah L. Jones[1]; Eckhard R. Podack[1]; Margaret A. Fischl[1]

[1]University of Miami, Miami, FL, US; [2]University of Miami, Miami, FL, US

Background: Human gamma delta (GD) T cells are essential components of the adaptive and innate immune system and play a well-documented role in epithelial barrier protection and tumor surveillance. Two subsets of GD T cells, defined by the use of either the V delta 2 (D2) or V delta 1 (D1) TCR, predominate. The majority of the circulating GD T cells bear V D2 TCR while the majority of the tissue-associated GD T cells are D1.

We hypothesized that, being the major component of intraepithelial mucosal compartment, endocervical GD T cells may have a decisive role in HIV infection and could help to control HIV replication. This study evaluates GD T cells in endocervical samples from women with and without HIV infection.

Methods: HIV infected (n=6) and HIV uninfected (n=7) pre-menopausal women participating in the WIHS cohort were recruited. Participants underwent vaginal examination with collection of endocervical cytobrushes and peripheral blood. Frequency and phenotype of CD3+ T lymphocytes and GD T cells were determined in cervical cytobrush samples and peripheral blood by multicolor flow cytometry.

Results: We found GD2 T cells are predominant GD T subset in the blood of HIV uninfected women (GD2 vs GD1 ratio 2.37±0.90), while we observed significant depletion of GD 2 T cells in the blood of HIV infected women (0.07±0.027). In contrast, only GD1 T cells were readily detected in the endocervical samples in both, HIV infected (GD2 vs GD1 ratio 0.03±0.01) and uninfected women (0.028±0.01). In the HIV infected women, we found significant decrease in the frequency of cervical GD1 T cells compared to HIV uninfected

women (19.78%±7.64 vs 54.29 %±10.05; p=0.02). Interestingly, in the HIV infected women the ratio of alpha beta to gamma delta T cells was significantly increased compared to HIV negative women (3.16±1.45 *vs* 0.42±0.17, p=0.04).

Conclusions: Current knowledge of the immune dynamics at the female reproductive tract is limited at best. We report for the first time, the unique GD1 T cells are a predominant T cell subset within cervical mononuclear cells. By eliminating cervical GD1, HIV cripples an important antiviral effector subset and removes a normal control over inflammation resulting in HIV persistence and progressing disease. We propose that evaluation of GD T cell responses could be used as a novel marker of mucosal vulnerability in women with HIV infection or at risk for HIV.

Funded by WHIS (U01 AI103397) and Miami CFAR (*P30AI073961).*

274 T Regulatory Cells Disrupt the CCL20-CCR6 Axis Driving Th17 Homing to the Gut

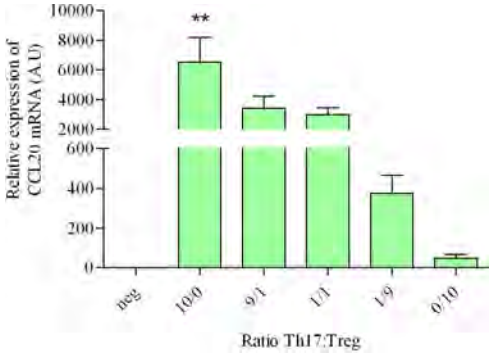
Claire Loiseau[1]; Mary Requena[1]; Michelle Cazabat[1]; Nicolas Carrere[2]; Bertrand Suc[2]; Bruno Marchou[2]; Jacques Izopet[1]; Pierre Delobel[1]
[1]Inserm, Toulouse, France; [2]Centre Hospitalier Universitaire de Toulouse, Toulouse, France

Background: During HIV-1 infection, the integrity of the intestinal immune barrier is disrupted due to a deep depletion of $CD4^+$ T cells in the gut, including Th17 cells, a T cell subset exerting a major role in antimicrobial immunity. The translocation of microbial products from the gut lumen into the bloodstream, associated with Th17 cells loss, has been linked with systemic inflammation. Despite effective cART, $CD4^+$ T cells in the *lamina propria* are incompletely restored in most individuals. The CCL20-CCR6 axis drives Th17 cells trafficking to the gut. We thus assess the factors regulating the expression of CCL20 by the enterocytes, and notably the role of the cytokines produced by Treg and Th17 cells.

Methods: Small bowell biopsies were obtained by endoscopy in 20 HIV-infected individuals. All of them had prolonged suppression of HIV-1 RNA in the plasma <50 copies/mL under cART for about 5 years. Their median level of blood $CD4^+$ T cells was of 668 cells/μL. Ten healthy HIV-1-negative individuals were used as controls. *CCL20* mRNA was quantified by qRT-PCR.

To explore the factors regulating CCL20 expression by the enteroyctes, we developped an *ex-vivo* system of human primary enterocytes (obtained from small bowel surgical resections of HIV-negative individuals) cultured as a tight monolayer on transwells. The effect of IL-17, IL-10, and TGF-β1 on CCL20 expression was assessed. A coculture was done between the enterocytes and various proportions of Th17/Treg cells, sorted from PBMCs on the basis of their $CD4^+CXCR3^-CCR6^+$ and $CD4^+CD127^{low}CD49d^-$ phenotype respectively (StemCell), and activated by PMA/ionomycin. The expression of CCL20 by the enterocytes was evaluated by qRT-PCR and ELISA.

Results: In small bowell biopsies of HIV-infected individuals receiving effective cART, *CCL20* mRNA was significantly reduced compared to healthy controls ($P < 0.05$). *Ex-vivo* on human primary enterocytes, IL-17A increases CCL20 expression whereas both IL-10 and TGF-β1 reduce it. In coculture expriments, CCL20 expression decreases as the Th17/Treg ratio skews from Th17 to Treg cells (Figure 1).



Conclusions: The CCL20-CCR6 axis driving Th17 cells gut homing is altered in HIV-infected individuals despite effective cART. A persistently imbalanced Th17/Treg ratio in the *lamina proria* could contribute to the reduced production of CCL20 by the enterocytes despite an effective cART. A vicious circle could arise between low CCL20 expression and the defective gut-homing of $CD4^+$ T cells, notably Th17 cells.

WEDNESDAY, FEBRUARY 25, 2015

Session P-C3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Innate and Unconventional T-Cell Responses

275 Effect of KIR2D-Mediated Immunity on Clinical Outcome Among CRF01_AE-Infected Thais

Masahiko Mori[1]; Nuanjun Wichukchinda[2]; Reiko Miyahara[1]; Archawin Rojanawiwat[2]; Panita Pathipvanich[3]; Toshiyuki Miura[1]; Michio Yasunami[1]; Koya Ariyoshi[1]; Pathom Sawanpanyalert[2]
[1]Institute of Tropical Medicine, Nagasaki University, Nagasaki City, Japan; [2]Ministry of Public Health, Nonthaburi, Thailand; [3]Day Care Centre, Lampang Hospital, Lampang, Thailand

Background: Class I human leukocyte antigen (HLA) molecule contributes to the immune control of HIV through antigen presentation to both cytotoxic T lymphocytes (CTL) and natural killer cells (NK). CTL contribution to HIV control through antigen presentation by protective HLA alleles, such as HLA-B*57 and HLA-B*27, has been studied well previously. However, reports on the NK cell contribution, with the exception of the protective effect of HLA-Bw4 and its ligand killer immunoglobulin-like receptor (KIR) 3DL1 and 3DS1 in HIV disease, are limited. In particular, studies about HLA-C-KIR2D on HIV control remain sparse.

Methods: 209 HIV-1 CRF01_AE-infected treatment-naïve Thais were recruited, and the effects of HLA-C-KIR2D on clinical outcome were statistically analyzed.

Results: 1) HLA-B*46:01, which worked as an HLA-C1 allele binding the same type of ligands despite being an HLA-B allele, was identified as the most predominant HLA-B allele (29% in the population frequency). 2) In the analysis of the viral set point difference among HLA-C1-positive individuals, subjects with KIR2DL3 had significantly higher set point compared to the subjects without KIR2DL3 (median 4.8 vs 4.2 log copies/ml, p=0.033 by Mann-Whitney U-test). 3) In multivariate analysis, the number of HLA-C1-KIR2DL3 associations (ranging from subjects having no HLA-C1-KIR2DL3 associations to subjects having up to four combinations; the KIR2DL3-positive individuals with HLA-B*46:01

homozygous and HLA-C1 allele homozygous) was identified as a significant viral load predictor (β=0.13, p=0.039 by linear regression model). 4) In longitudinal analysis, higher mortality rate was identified among the subjects with higher number of HLA-C1-KIR2DL3 associations (p=0.002 by log rank test; aHR=2.0, 95% CI 1.3-3.2, p=0.004 by Cox hazard model) (Figure). 5) However, no advantage of HLA-Bw4-KIR3DL1/S1 on clinical outcome was found in this cohort.

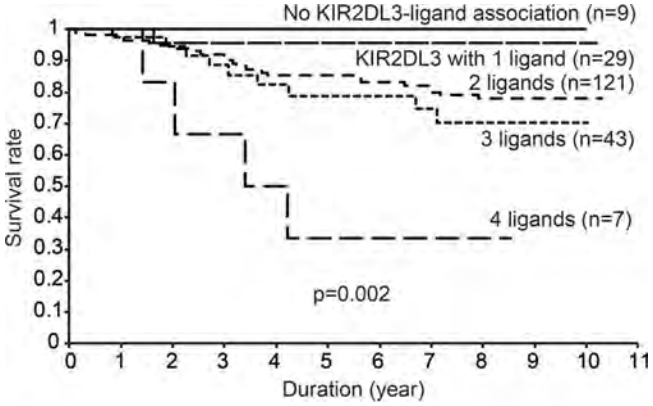


Figure. The number of KIR2DL3-ligand HLA associations and survival rate analysis, log rank test.

Conclusions: In this study, the effects of HLA-C and KIR2D interaction with a focus on the effect of the detrimental HLA-C1-KIR2DL3 association, on clinical outcome among HIV-1 CRF01_AE-infected Thais were investigated. These findings will impact the existence of the unique anti-HIV innate immune pressure and viral adaptation to such pressure in each endemic area.

276 HLA-KIR-Associated Sites in Gag and Their Effects on Clinical Outcome in Thailand

Masahiko Mori[1]; Nuanjun Wichukchinda[2]; Reiko Miyahara[1]; Archawin Rojanawiwat[2]; Panita Pathipvanich[3]; Toshiyuki Miura[1]; Michio Yasunami[1]; Koya Ariyoshi[1]; Pathom Sawanpanyalert[2]

[1]Institute of Tropical Medicine, Nagasaki University, Nagasaki City, Japan; [2]Ministry of Public Health, Nonthaburi, Thailand; [3]Day Care Centre, Lampang Hospital, Lampang, Thailand

Background: Viral peptides (epitope) are presented by class I HLA molecules to both cytotoxic T lymphocyte (CTL) through T cell receptor (TCR), and natural killer (NK) cell through killer immunoglobulin-like receptor (KIR). Compared to the studies about anti-HIV immune pressure by CTL and its related viral adaptation, studies about NK cell remain sparse.

Methods: 208 HIV-1 CRF01_AE-infected treatment naïve Thais were recruited. Their clade I HLA allele, KIR, viral load, and Gag sequence data were collected, and 1) HLA-KIR-associated Gag mutation or preservation sites by Fisher's exact test with 95% confidential interval, 2) effects of HLA-KIR-associated sites on viral load by Mann-Whitney U-test, 3) correlation between the number of associated sites and viral load by Spearman's correlation test, and 4) the number of associated sites and survival rate by log rank test and Cox hazard model, were analyzed.

Results: 1) 52 HLA-KIR-associated sites (20 sites at p17, 15 sites at p24, and 17 sites at p15) were identified, 2) 6 out of 52 sites also scored viral load difference between association positives and negatives with significance; 4 out of 6 sites scored lower viral load among associated mutation positives, suggesting viral escape mutations with lower viral set point by HLA-KIR-derived immune pressure. 3) Negative correlation between the number of mutation at above 4 protective sites and viral load was identified (r=-0.18, p=0.0023). Among 4 sites, 3 sites were HLA-Bw4-KIR3DL1-associated mutations (I104X, N252X, and T454X). Finally in longitudinal analysis, 4) Among HLA-Bw4-KIR3DL1 positives, higher number of HLA-Bw4-KIR3DL1-associated mutations also scored higher survival rate (p=0.0088 by log rank test (Figure), and 0.63 (0.47-0.84) of hazard ratio (95% CI), p=0.002 by Cox hazard model).

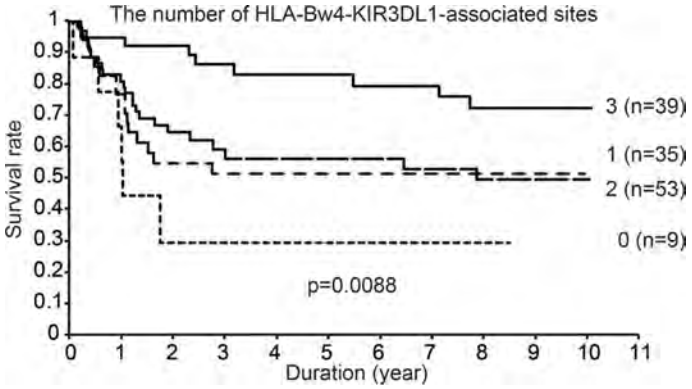


Figure. The number of HLA-Bw4-KIR3DL1-associated sites and survival rate analysis, by log rank test. Survival rate difference among the groups of HLA-Bw4-KIR3DL1-associated sites number (from 0 to 3) are shown. All n=136 subjects are HLA-Bw4+KIR3DL1+.

Conclusions: KIR-HLA-associated sites in Gag were identified, and several sites were strongly associated with clinical outcomes by cross sectional and longitudinal analysis. These findings imply the existence of immune pressure by NK cell and consequent viral adaptation. These findings will contribute to further development of epitope-based vaccine study.

277 In KIR3DL1/S1 Heterozygotes Are KIR3DL1 and KIR3DS1 Co-Dominantly Expressed?

Zahra Kiani[1]; Nicole F. Bernard[1]; Julie Bruneau[2]

[1]McGill University, Montreal, Canada; [2]Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Montreal, Canada

Background: Epidemiological studies show that co-carriage of *KIR3DS1* (*3DS1*) and a subset of *HLA-Bw4* alleles with an isoleucine at position 80 of the HLA heavy chain (*3DS1+*80I*) is associated with slow time to AIDS. NK cells from *3DS1+*80I* carriers have high anti-HIV activity. There is conflicting information regarding whether NK cells from *KIR3DL1/S1* heterozygotes (htz) exhibit allelic exclusion or co-dominance in terms of expression of the NK cell receptors 3DS1 and KIR3DL1 (3DL1). Monoclonal antibody (mAb) Z27

binds 3DL1 with a high and 3DS1 with a low intensity. Z27 staining cannot distinguish whether Z27^{high} NK cells express 3DL1 only or include NK cells that also express 3DS1. We developed an approach to address this question.

Methods: Peripheral blood mononuclear cells from *3DL1/S1*htz and, as controls, *3DL1* and *3DS1* homozygotes were stained with anti-CD3, anti-CD56 and Z27. CD3^{-}CD56^{+} NK cells were sorted into Z27^{high}, Z27^{dim} and Z27^{neg} sub-populations. RNA was extracted from each subset and cDNA was prepared from RNA. Real-time (RT)-PCR was used to determine the presence or absence of *3DS1* and *3DL1* transcripts in sorted cells.

Results: First, we verified the specificity of *3DS1*, *3DL1* primer sets. We verified that the sorting gates distinguishing Z27^{dim} from Z27^{neg} populations were correctly set by showing that no *3DS1* transcripts were present in the Z27^{neg} subset from either *3DS1*hmz or *3DL1/S1*htz. Using RT- PCR and the *3DS1* specific primers we found that the Z27^{dim} subset of *3DS1*hmz and both the Z27^{dim} and Z27^{high} subsets of *3DL1/S1*htz amplified *3DS1* transcripts. We found *3DL1* primers amplified transcripts from Z27^{high}, but not from the Z27^{dim} subset of *3DL1/S1*htz.

Conclusions: 3DL1 and 3DS1 can be co-dominantly expressed on NK cells. The accepted theoretical paradigm posits that engagement of the inhibitory 3DL1 NK receptor by its ligand, HLA-Bw4, is important in licensing NK cells for function. Engagement of the activating 3DS1 NK receptor should tune down the potency of NK cell licensing and the functional potential of 3DS1+ NK cells. This raises questions regarding the mechanism underlying the association between *3DS1+*80I* carriage and HIV control. Our results provide a framework for improving our understanding of the role played by the 3DL1 and 3DS1 receptors in determining the function of NK cell subsets in general and the anti-HIV function of these cells in particular.

278 Disruption of Innate-Like Unconventional T-Cell Subsets in HIV-Infected Children

Alka Khaitan[1]; Adam Kravietz[1]; Ilmet Tiina[1]; Mussa Mwamzuka[2]; Fatma Marshed[2]; Cihan Tastan[1]; Aabid Ahmed[2]; Bill Borkowsky[1]; Derya Unutmaz[1]
[1]New York University School of Medicine, New York, NY, US; [2]Bomu Hospital, Mombasa, Kenya; [3]New York University School of Medicine, New York, NY, US

Background: A subset of T cells comprised of mucosal associated invariant T (MAIT), natural killer T (NKT), and γδ T cells exhibit features of innate cells such as invariant TCR and recognition of non-peptide antigens. These unconventional T cell subsets can secrete pro-inflammatory cytokines or display cytotoxic activity in response to bacterial and fungal derived glycolipids or metabolites. HIV+ adults have lower MAIT and NKT and higher γδ T cells in the peripheral blood. Less is known about their changes in HIV-infected children. We sought to determine whether innate-like T cells are disrupted in treated and untreated HIV+ children.

Methods: We evaluated peripheral blood samples of 76 perinatally-infected HIV+ and 40 HIV- children between 3-12 years old from Mombasa, Kenya. The HIV+ cohort included 39 ART naïve (ART-) and 37 children on ART (ART+). Cryopreserved PBMCs were thawed and stained with surface antibodies CD3, CD4 and CD8 with Vα7.2 and CD161 (MAIT), γδ TCR, and Vα24Jα18 TCR (NKT) then analyzed by flow cytometry. Plasma sCD14 was measured by ELISA. Statistical analysis was performed on GraphPad Prism with Mann-Whitney or Spearman's correlation tests.

Results: HIV+ children had decreased levels of MAIT in CD8+ T cells (ART- p=0.0156; ART+ p=0.0137), which correlated positively with CD4:CD8 ratios (r=0.37, p=0.0018). ART+ had lower MAIT levels in CD4+ T cells (p=0.0090); both HIV+ groups maintained CD4-CD8- MAIT cell frequencies and MAIT cell numbers in total T cells. Plasma sCD14 levels were higher in HIV+ (p=0.0068). In HIV+ children CD8+ MAIT cells inversely correlated with sCD14 (r= -0.33, p=0.0049). NKT cells were also lower in ART- (p=0.0001) and ART+ (p=0.0140) and correlated with CD4:CD8 (r=0.25, p=0.0417). Conversely, γδ T cells were persistently elevated in HIV+ (ART- p=0.0064; ART+ p<0.0001) and correlated positively with sCD14 (r=0.36, p=0.0025). Interestingly, in HIV+ children γδ T cells negatively correlated with CD8+ MAIT (r= -0.36, p=0.0024) and NKT (r= -0.27, p=0.0063) cells and the ratio of γδT/MAIT cells positively correlated with sCD14 (r=.0.37, p=0.0019).

Conclusions: CD8+ MAIT and NKT cells are relatively lower in HIV+ children despite ART compared to HIV- children. This decline in innate-like T cells worsens with diminished immune status. Loss of MAIT cells from the periphery may reflect migration to mucosal tissues in response to microbial translocation. Increases in γδ T cells may be a compensatory response to decreased MAIT and NKT cells in HIV infected children.

279 HIV-1 Alters Innate Immune Response to BCG, Which Differs From SIV Infected Mangabeys

Melanie Gasper; David Sherman; **Donald Sodora**
Seattle Biomed, Seattle, WA, US

Background: Coinfection with *M. tuberculosis,* as well as other *Mycobacteria,* is a leading cause of morbidity and mortality for HIV-infected patients. Here we set out to understand functional immune responses to an opportunistic pathogen, *M.bovis BCG*, during both pathogenic HIV and non-pathogenic SIV infections (natural SIV host sooty mangabeys). *M. Bovis BCG* is a live-attenuated vaccine strain of Mycobacteria, which has demonstrated opportunistic potential.

Methods: Multiparameter flow cytometry and gene expression analysis, utilizing a Nanostring platform (248 genes), was used to evaluate the ability of monocytes and peripheral blood mononuclear cells (PBMC) to respond to 4 hour *ex vivo* BCG stimulation. KEGG analysis was used to identify pathways altered by changes in gene expression. Uninfected and HIV/SIV infected humans and sooty mangabeys were analyzed.

Results: HIV infection was associated with a reduced percentage of whole blood monocytes producing IL-12 in response to BCG (1.8% compared to 4% in uninfected donors; p=0.02). In contrast, SIV+ mangabeys had a higher percentage of monocytes producing IL-12 and TNF-α in response to BCG compared to uninfected mangabeys, suggesting a maintained immune response. In addition, principal component analysis showed that although both species mounted a robust response to BCG, HIV-infected donors had a unique BCG-induced gene expression profile that distinguished them from uninfected age-matched donors. In contrast, SIV-infection status did not alter the gene expression clustering pattern between SIV+ and SIV- mangabeys. KEGG analysis demonstrated that genes with increased expression at baseline in HIV+ donors were significantly enriched within the NK cell cytotoxicity pathway (hypergeometric test; p=0.007), this difference was not seen between SIVneg and SIV+ mangabeys. Additionally, a statistical interaction between HIV disease status and the response to BCG was found in a number of genes related to NK cell function, including NKp46, IFNg and perforin, suggesting that HIV-infection altered the NK cell response to bacterial stimulation.

Conclusions: Overall, these data provide evidence that innate immune responses (including monocyte IL-12 production and NK cell activity) to the BCG opportunistic pathogen are likely to be critical for resistance to opportunistic infections following lentiviral (HIV/SIV) infection.

280 High-Level Replication Allows SHIVs to Overcome the Macaque Interferon Response

David F. Boyd; Amit Sharma; Julie M. Overbaugh
Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US

Background: SIV/HIV chimeric viruses (SHIVs) encoding HIV-1 envelope (Env) have been studied in macaques as models of HIV-1 infection in humans. Typically, the initial chimeric SHIVs generated *in vitro* replicate poorly in macaques, but a subset has been successfully adapted to replicate in macaques through animal passage. The resulting SHIVs cause persistent infection in macaques that mimics many aspects of pathogenic HIV-1 infection. The SHIV/macaque model is limited because the few pathogenic SHIVs currently in use

require adaptation after infection of macaques and do not represent the diversity of circulating HIV-1 variants. Type-I interferon (IFN) is an innate immune factor that induces multiple host restriction factors that could contribute to poor replication of SHIVs, and the role of IFN in SHIV replication in macaques has not been well defined.

Methods: We examined 8 SHIVs, including 3 representing pathogenic SHIVs adapted for replication in macaques, 1 SHIV encoding culture-adapted HIV-1, and 4 SHIVs encoding HIV-1 Envs representing circulating variants for the ability to replicate in macaque lymphocytes. During a 12-day time course, we measured viral replication kinetics during the logarithmic growth phase and sensitivity to IFN for each SHIV.

Results: We found that the SHIVs tested exhibited a range of replication kinetics and that the mean replication slope of SHIVs encoding Envs adapted in culture or in macaques was significantly greater than that of SHIVs encoding Envs from circulating variants (1.01 vs. 0.74, $p = 0.03$). We also found that replication slope positively correlated with resistance to IFN treatment (Spearman $r = 0.88$, $p = 0.007$). By generating chimeras between a pathogenic SHIV and one derived from a circulating HIV-1 variant, we found that high replication kinetics and resistance to IFN treatment mapped to HIV-1 Env.

Conclusions: The findings of this study indicate that HIV-1 Env is a major viral determinant of high replication kinetics of SHIVs in macaque cells and that replication kinetics play an important role in the ability of SHIVs to overcome the IFN response. SHIVs that have been adapted in macaques exhibit high replication kinetics and resistance to IFN, which may contribute to their ability to establish persistent infection in macaques. These studies suggest the presence of an IFN-induced factor(s) that can be antagonized by Envs that facilitate rapid replication.

281 Elevated IFN-γ in HIV Patients Using a Novel Assay for Adaptive and Innate Immunity

Michelle K. Yong[1]; Paul Cameron[1]; Tim Spelman[2]; Julian Elliott[1]; Christopher Fairley[4]; Jeffrey Boyle[3]; Misato Miyamasu[3]; Sharon R. Lewin[1]

[1]Monash University/Alfred Hospital, Melbourne, Australia; [2]Burnet Institute, Melbourne, Australia; [3]Qiagen, Melbourne, Australia; [4]Melbourne Sexual Health Centre, Melbourne, Australia

Background: HIV infection is characterised by immune activation of both the adaptive and innate immune responses that persists in patients following antiretroviral therapy (ART) and has been associated with poor CD4+ T-cell recovery and serious non-AIDS events (SNAE). The aim of this study was to evaluate adaptive and innate immunity in HIV-infected patients prior to and following ART.

Methods: A cross sectional study of HIV and non-HIV infected individuals were recruited from The Alfred Hospital and the Melbourne Sexual Health Centre (MSHC), Melbourne Australia. HIV-infected patients were either naïve to ART or on suppressive ART for 12 months. Whole blood was assessed using the Quantiferon Monitor (QFM) assay containing 1:1 IU/ml of anti-CD3 (T-cell receptor ligand) and R848 (TLR7 ligand). We also assessed 0.1:0.1 IU/ml of anti-CD3 and R848 (QFM 1:10). Production of IFN-γ levels (IU/mL) was measured in supernatant by ELISA.

Results: We recruited HIV-infected participants (n=79; n=20 naïve to ART and n=59 on suppressive ART; median CD4 of 557 cells/μl (IQR 403-729 cells/μl) and median age of 45 years (IQR 34-55 years) and healthy controls (n=229). HIV-infected participants on ART were older (47 vs 31 years, $p<0.001$) and had a longer duration of HIV infection (12.3 vs 1.4 years, $p=0.004$). IFN-γ production with QFM 1:10 was significantly higher in HIV infected patients compared to healthy controls (median IFN-γ 512 vs 223 IU/ml, $p<0.0001$), and this difference remained whether in participants both on or off ART (median IFN- γ 512 and 593 IU/ml respectively, K-Wallis test of difference $p=0.0004$). IFN-γ production in patients on ART was significantly higher in participants with CD4 >350 cells/μL compared to a CD4<350 cells/μL (561 vs 259 IFN IU/ml $p=0.02$). Patients with CD4 counts <350 had responses similar to healthy controls. IFN-γ production was significantly higher in male HIV-infected patients (median IFN 542 vs 77 IU/ml $p=0.02$). There were no known associations between IFN responses and age ($p=1.0$), viral load ($p=0.56$), nadir CD4 count ($p=0.6$) or duration of HIV infection ($p=0.18$). Using a multivariable analysis with 6 variables, neither CD4 nor sex were independently predictive of IFN-γ production.

Conclusions: Using a high throughput assay which assesses both adaptive and innate immunity, we show marked increases in IFN-γ production in HIV-infected patients both on and off ART. Further research is warranted to determine if changes in Quantiferon Monitor are also associated with SNAEs.

282 TLR8 Regulation of LILRA3 Is Abrogated in HIV Infection and Correlates to CD4 Counts and Virus Loads

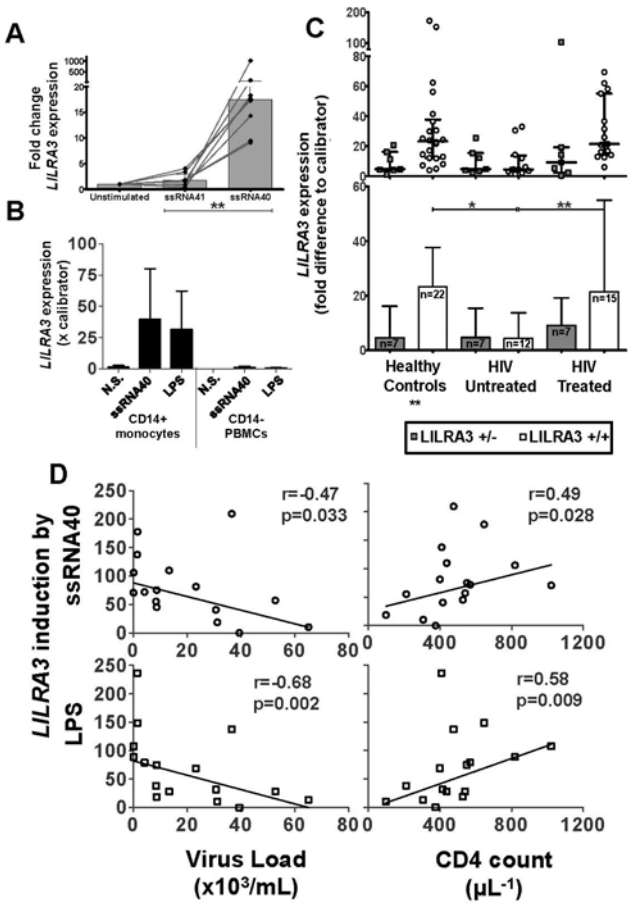
Hui Zhi Low; Gerrit Ahrenstorf; Torsten Witte

Hannover Medical School, Hannover, Germany

Background: LILRA3 is an immunostimulatory molecule which conditionally induces proliferation in CD8+ T-cells and NK-cells via the stimulation of monocytes. LILRA3 has a deletion allele whose presence is a risk factor for HIV. Therefore, we believe that LILRA3 plays a role in viral immunity and want to study how LILRA3 is regulated.

Methods: From a panel of TLR agonists, ssRNA40 is a major inducer of *LILRA3* (not shown). To confirm this, we used ssRNA41 as additional control and studied this regulation in 8 donors. We magnetically isolated $CD14^+$ monocytes after stimulation and analyzed *LILRA3* levels in both $CD14^+$ and $CD14^-$ populations (n=3). Monocytes of healthy donors (n=29), HIV-untreated (n=19) and HIV-treated (n=22) patients were stimulated with ssRNA40 and analyzed for *LILRA3*. Cohorts were segregated according to genotype ($LILRA3^{+/+}$ and $LILRA3^{+/-}$). Mann-Whitney test was used for intra-group *LILRA3* expression. Kruskal-Wallis test was used for inter-group *LILRA3* expression among $LILRA3^{+/+}$. In a second cohort, monocytes of healthy donors (n=13), HIV-untreated (n=16) and HIV-treated (n=11) patients received ssRNA40 or LPS (100 ng/mL). One-tailed Spearman analysis was used to calculate correlation between *LILRA3* expression and virus loads and CD4 counts.

Results: TLR8 agonist ssRNA40 is a potent inducer of *LILRA3* (Figure 1A). This process occurs mainly in monocytes (Figure 1B). By segregation of cohorts into *LILRA3* genotypes, we observed that ssRNA40-induced *LILRA3* is dependent upon its gene dosage, with heterozygotes expressing less *LILRA3* (Figure 1C). Among the $LILRA3^{+/+}$ donors, the TLR8-induced *LILRA3* in HIV untreated patients was abrogated in comparison to the robust responses of healthy controls. LPS induced less *LILRA3* than ssRNA40 among healthy controls (not shown), but remain at similar low levels for HIV untreated patients. We hypothesized that LILRA3 is helpful in controlling virus infections and that ssRNA40 and/or LPS induction of *LILRA3* should correlate negatively to virus load and positively to CD4 counts, and indeed they do in untreated patients (Figure 1D). Finally, LILRA3 itself can induce a host of proinflammatory genes and can alter the antigen presentation machinery of monocytes (not shown).



Conclusions: In conclusion, our experiments supported the beneficial role of LILRA3 in virus infections, in particular for ssRNA viruses, like HIV, that engage TLR8. These findings indicate considerable potential for exploring the use of LILRA3 in the treatment of virus infection.

WEDNESDAY, FEBRUARY 25, 2015

Session P-C4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Monocytes, Dendritic Cells, and Neutrophils

283 Siglec-1 on Monocytes From Untreated HIV-1–Infected Patients Enhances HIV-1 Transfer

Maria Pino; Susana Benet; Itziar Erkizia; Judith Dalmau; Dan Ouchi; Bonaventura Clotet; Javier Martínez-Picado; Nuria Izquierdo-Useros

IrsiCaixa Institute for AIDS Research, Badalona, Spain

Background: The IFNα-inducible receptor Siglec-1 (CD169) is expressed on myeloid cells and recognizes HIV-1 membrane gangliosides, enhancing viral uptake and cell-to-cell transmission. Moreover, Siglec-1 is upregulated on monocytes of HIV-1-infected-individuals with high viral loads. However, if Siglec-1 expressed on monocytes from HIV-1-infected patients mediates viral transmission is still unknown. Here, we aim to study the role of Siglec-1 in HIV-1 transfer on primary monocytes isolated from HIV-1 infected patients.

Methods: We assessed Siglec-1 expression on monocytes from HIV-1-infected individuals before and after antiretroviral treatment and IFNα-treated monocytes from seronegative donors by FACS. $P24^{Gag}$ ELISA and a luciferase-reporter cell line were used to assess monocyte-mediated HIV-1 uptake and transmission. mAb α-Siglec-1 was used to study specific HIV-1 recognition via Siglec-1. Siglec-1 induction was analyzed by FACS on myeloid cells cultured with plasmas from HIV-1-infected individuals, and blocked with the type I IFN recombinant protein B18R. Statistical analyses were performed using paired t-test (*P*) and Pearson correlation (ρ).

Results: IFNα-treated monocytes have an enhanced ability to capture and trans-infect HIV-1 via Siglec-1 recognition. Siglec-1 expression was higher on monocytes isolated before antiretroviral treatment that also exhibited a higher HIV-1 uptake and HIV-1 transmission capacity compared to monocytes obtained under suppressive therapy ($P \leq 0.0117$). Consistently, plasmas of untreated HIV-1-infected individuals triggered higher Siglec-1 expression on myeloid cells compared to plasmas from the same individuals, but obtained after antiretroviral treatment. Furthermore, Siglec-1 induction could be blocked by the neutralizing/decoy type I IFN receptor B18R ($P<0.0001$). Finally, we found a positive correlation between Siglec-1 expression levels on isolated monocytes from treatment-naïve patients and i) HIV-1 uptake ($\rho = 0.8$), ii) HIV-1 trans-infection capacity ($\rho = 0.78$) and iii) plasma viral load ($\rho = 0.66$).

Conclusions: These results indicate that *in vivo*, Siglec-1 expression on peripheral blood monocytes is upregulated by HIV-1 infection, but normalizes after effective antiretroviral treatment. Soluble activation factors from plasma of these patients induced Siglec-1 expression on myeloid cells via type I IFN receptor signaling. Furthermore, Siglec-1 on monocytes enhances HIV-1 cell-to-cell transmission, indicating that this receptor could impact HIV-1 pathogenesis.

284 Soluble CD40 Ligand Contributes to Dendritic Cell Mediated T-Cell Dysfunction

Elizabeth A. Miller; Ramya Gopal; Vanessa Valdes; Jeffrey S. Berger; Nina Bhardwaj; **Meagan O'Brien**
Icahn School of Medicine at Mount Sinai, New York, NY, US

Background: Soluble CD40 ligand (sCD40L) levels are increased during human immunodeficiency virus (HIV) infection, but it is unknown whether monomeric or multimeric forms predominate, and whether there are differential effects of these forms on dendritic cell function and dendritic cell-T cell interactions.

Methods: Immunoblots were performed to delineate various forms of sCD40L present in plasma from HIV-infected donors. Monocyte-derived DCs (moDCs) from seronegative donors were exposed to forms of sCD40L prior to Toll-like receptor (TLR) stimulation and moDC function and T cell function was assessed *in vitro*. Levels of sCD40L in plasma from ART-treated HIV-infected donors before and after low dose aspirin therapy were measured via ELISA.

Results: Multiple forms of sCD40L were identified in plasma from ART-treated HIV-infected donors, including monomers, dimers, and trimers. Though monomeric and multimeric forms of sCD40L had differential effects on DC activation when given alone, both strongly suppressed secretion of the Th1 skewing cytokine, IL-12, upon subsequent TLR stimulation. Furthermore, moDC exposed to both monomeric and multimeric sCD40L induced T cell anergy and regulatory T cell formation. One week of low dose aspirin decreased sCD40L in ART-treated HIV infected subjects, suggesting that heightened sCD40L is due in part to platelet activation and is responsive to anti-platelet therapy.

Conclusions: Elevated sCD40L during HIV infection contributes to dendritic cell mediated T cell dysfunction. Anti-platelet agents that decrease sCD40L may provide immune modulatory benefits as adjunctive therapies to ART.

285 The Alarmin HMGB1 Is Crucial for the Acquisition of Antiviral pDC Effector Functions

Hela Saïdi[1]; Marlène Bras[1]; Pauline Formaglio[1]; Bruno Charbit[1]; Marie-Thérèse Melki[2]; Marie-Lise Gougeon[1]
On behalf of the Antiviral Immunity, Biotherapy and Vaccine Unit
[1]*Institut Pasteur, Paris, France;* [2]*Sebia, Evry, France*

Background: Plasmacytoid dendritic cells (pDCs) are the main producers of interferon-alpha (IFNα), a powerful innate antiviral cytokine. IFNα production by pDCs is promoted by their cross-talk with NK cells, which triggers NK cell-cytotoxicity through the up-regulation of the death ligand TRAIL. HIV-1 directly activates pDCs by inducing their maturation and their production of IFNα. HIV-1 is also involved in the differentiation of pDCs into TRAIL-expressing killer cells. The impact of NK cells on IFN-a-production and TRAIL-expression by pDCs in the context of HIV-1 infection is unknown. Given the essential role of both pDCs and NK cells in the control of HIV-1 infection, the objective of this study was to determine the impact of NK-pDC cross-talk on the reciprocal triggering of antiviral activities.

Methods: pDCs and NK cells were negatively sorted from PBMC of healthy donors. NK cells were kept either unstimulated (rNK) or activated with PMA/ionomycin for 2 hrs (aNK). pDCs were either uninfected or infected with R5-HIV-1 BAL (pDC_{HIV}) at various concentrations and co-cultured with NK cells at different ratios for 24 h. The fate of both cell types was studied using multiparametric flow cytometry combined to Multianalyte Profiling technology and Gene array approach.

Results: HIV-1 infection of primary pDCs induces the expression of maturation markers (HLA-DR, CD80, CD83, CD86) and the homing receptor CCR7. It also induces the emergence of TRAIL-expressing IFNα-producing pDCs in a dose-dependent manner. At low concentrations of HIV-1, the crosstalk of pDC_{HIV} with aNK cells significantly increased the production of IFN-a, the proinflammatory mediators IL-12, TNF-a and IFN-g and the b-chemokines MIP-1 a and MIP-1 b. It also triggered TRAIL expression on NK cells. At high concentrations of HIV-1, NK cells did not significantly modulate the production of these cytokines and chemokines. Interestingly, the alarmin HMGB1 released by pDCs upon HIV-1 infection, plays an essential role during NK-pDC cross-talk, and its inhibition by Glycyrrhizin, N-Ethylpyruvate or anti-HMGB1 Abs prevented pDCs maturation, the release of IFNα and b-chemokines, and the emergence of TRAIL-expressing NK cells and pDCs.

Conclusions: These findings highlight the essential role of NK-pDC_{HIV} cross-talk in the acquisition of effector antiviral functions by pDCs and NK cells and reveal the essential role of HMGB1 during this crosstalk.

286 Dysfunctional Neutrophil Responses to SIV Infection

Tiffany Hensley-McBain[1]; Laura E. Richert-Spuhler[1]; Jillian Gile[1]; Melon T. Nega[2]; Thomas H. Vanderford[2]; Jacob D. Estes[3]; Brandon F. Keele[3]; Nichole R. Klatt[1]
[1]*University of Washington, Seattle, WA, US;* [2]*Emory University, Atlanta, GA, US;* [3]*Frederick National Laboratory for Cancer Research, Frederick, MD, US*

Background: Recent studies indicate that individuals with low neutrophils (PMN) are at increased risk of HIV infection. Also, the RV144 vaccine trial implicated non-neutralizing antibodies and associated Fc-mediated functions in vaccine-induced protection. These studies suggest that early innate antiviral functions and Fc-mediated functions of PMN may play an important role in mediating early viral control, yet the role of innate cellular responses in preventing the establishment of the viral reservoir remains unknown. The potential to contribute to the early control of viral spread may depend on the kinetics of PMN mobilization, activation, and recruitment during acute HIV/SIV infection.

Methods: We assessed kinetic changes in PMNs in peripheral and mucosal tissues during acute SIV infection in six rhesus macaques challenged i.r. with 100,000 TCID50 of SIVmac239X. Flow cytometry, CBC, and luminex were used to assess PMN and cytokine levels and related PMN functional markers. Samples were collected pre-SIV and days 3, 7, 14, 21, 28, 42, and 63 post-SIV.

Results: We observed trending decreases in systemic IL-17 ($p=0.0793$) and G-CSF ($p=0.0625$) early after SIV. In addition, we observed no increase in local IL-8 measured from rectal cytobrush supernatants after infection ($p=0.2751$). Surprisingly, blood PMN concentrations steadily decreased after infection, and no significant increase of PMN was detected in gut or lymphoid tissues. In addition, blood PMN numbers and rectal PMN percentages significantly correlated ($p=0.0032$). Lastly, HLA-DR ($p=0.0313$), CD86 ($p=0.0156$), and FcγRI ($p=0.0313$) were significantly upregulated on PMN during acute SIV infection.

Conclusions: In contrast to other acute viral infections, such as influenza, PMN-supporting cytokines and chemokines are decreased or not induced during acute SIV, potentially contributing to lack of PMN mobilization and recruitment to the tissues. Further, blood and rectum PMN levels correlate post-SIV, suggesting that blood PMN concentration may directly impact recruitment to gut tissues. Lastly, upregulation of markers involved in antigen presentation and Fc-mediated functions highlights the potential diverse functional roles of neutrophils during acute SIV infection and the mechanisms by which neutrophils, if induced, could contribute to more effective viral control. This may represent a mechanism of escape unique to retroviruses by which they dysregulate the cellular innate immune response during acute infection.

TUESDAY, FEBRUARY 24, 2015

Session P-C5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Studies of HIV-Exposed Uninfected Individuals

287 HIV-Exposed Seronegative MSM Have Increased Novel Antiviral Factors in Rectal Mucosa

Laura Romas[1]; Klara Hasselrot[2]; Kristina Broliden[2]; Carolina Herrera[3]; Garrett Westmacott[4]; Francis Plummer[4]; Terry B. Ball[4]; Adam Burgener[1]

[1]University of Manitoba, Winnipeg, Canada; [2]Karolinska Institutet, Stockholm, Sweden; [3]Imperial College London, London, United Kingdom; [4]Public Health Agency of Canada, Winnipeg, Canada

Background: HIV-Exposed Seronegative (HESN) individuals have shown altered mucosal immune responses in cervical, salivary and foreskin secretions associated with reduced HIV-susceptibility; however, this has not been investigated in rectal mucosa. As the rectal compartment is a major portal of entry for HIV understanding site-specific immune responses is important for biomedical prevention research. Advances in proteomic tools, such as mass spectrometry, allow for a comprehensive evaluation of several hundreds of immune factors within mucosal secretions. Here we perform the first proteomic analysis of rectal mucosal from HESN MSM identifying unique antiviral factors in this population.

Methods: Rectal lavage from HESN MSM (n=25) and non-exposed healthy controls (n=14) from the Venhälsan clinic, Sweden, were analysed by label-free tandem mass spectrometry. Identification of proteins, differential expression analysis and pathway analysis were performed. Several differentially expressed proteins that demonstrated innate expression were screened for HIV-neutralizing activity in PBMC and colorectal-explant culture and in the presence of R5- and X4-tropic HIV lab strains (HIV-Bal and HIV-3B, respectively) using p24 ELISA.

Results: HESN MSM overexpressed 25 immune proteins, including 3 antiproteases ($p<0.05$). These proteins did not show a significant correlation ($p>0.05$) with clinical variables (frequency oral/anal sex, HIV-neutralizing IgA, and VL of HIV+ partner). Pathway analysis linked overabundant proteins to the canonical pathway. One antiprotease (AP1) overabundant in HESN MSM demonstrated antiviral activity *in vitro*. Preliminary neutralization assays showed that "AP1" reduced Bal infection by a maximum of 61% and reduced IIIB infection by 90% (20 μg/ml) in PBMCs with negligible effect on cell viability (cell viability >60%, $p<0.05$); inhibition of HIV infection in rectal explants inhibited at a maximum of 75% (25 μg/ml).

Conclusions: HESN MSM overexpress an antiprotease with previously undescribed antiviral activity, which may contribute to reduced susceptibility to HIV at the rectal mucosa. This is likely a result of innate differences rather than HIV-exposure. Our findings overlap with previous studies of showing an overabundance of antiviral factors in the cervical secretions of HESN women, supporting further study into their roles in HIV infection. This knowledge is critical for the design of safe, effective HIV-prevention technologies for MSM.

288 PBMC From Highly Exposed Seronegative Individuals Inhibit Transmitted Founder HIV

Kevin C. Olivieri[1]; Eunyoung Kim[3]; Susan Little[5]; Michael Turchin[4]; Vanessa Serrano[1]; Amna Rasheed[2]; Quy Nguyen[1]; Paul Dejesus[1]; Steven Wolinsky[3]; Sumit Chanda[1]

[1]Sanford-Burnham Medical Research Institute, San Diego, CA, US; [2]University of California Los Angeles (UCLA), Los Angeles, CA, US; [3]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [4]University of Chicago, Chicago, IL, US; [5]University of California San Diego (UCSD), San Diego, CA, US

Background: Highly-exposed Sero-Negative (HESN) individuals engage frequently in unprotected sexual activities, yet remain sero-negative. In order to avoid sero-conversion, these individuals likely restrict HIV infection soon after transmission. Transmission of HIV infection is established by an extremely small fraction of circulating virus. These Transmitted Founder viruses (TFV) likely arise from a single HIV clone. Recently, Parrish and Fenton-May have shown that TFV are type I interferon (IFN)-resistant compared to chronic viruses from the same individual. We hypothesize that HESN inhibit TFV more efficiently than normal donors after IFN-beta treatment.

Methods: We examined the ability of PBMC from 23 normal donors and 32 HESN donors to inhibit 10 TFV or an R5-tropic NL4-3 derivative, JM1186 after IFN-beta treatment in 14 day in vitro assays. p24 concentration was determined by alpha-LISA. HESN PBMC genotypes for selected genes were performed by custom Nimblegen Array and 454 Sequencing.

Results: After low dose IFN treatment, a significant proportion of HESN, but not normal, PBMC inhibited JM1186 infection >25% ($p = 0.0017$). In a separate assay, 12 HESN PBMC and 8 normal PBMC were infected with TF CH040, TF SUMA, TF CH058, 6 month chronic virus (6mo) CH058, and JM1186 and treated or not with 75 IU/ml IFN-beta. In untreated samples, only infection with TF CH058 resulted in a significantly lower p24 in HESN ($p = 0.0473$). Interestingly, this virus does not trigger an IFN response in normal monocyte-derived dendritic cells. In normal PBMC, the TFV CH040 and SUMA were more resistant to IFN-beta than JM1186 ($p = 0.0031$ and 0.0446, respectively). For HESN samples, the median level of IFN-beta inhibition for all viruses was lower than normal, significantly so for CH040 and SUMA, ($p = 0.0027$ and 0.0181, respectively). All samples were ranked for their ability to inhibit all viruses. 6 of 9 HESN donors with ranks above the distribution of normal donors had variations in genes that were reported to interact with HIV Protease, Vpr, Vpu, Integrase, and Env.

Conclusions: PBMC from HESN respond to IFN in a manner that more efficiently inhibits some viruses, including two TFV. HESN appear able to also inhibit an IFN sensitive TFV without IFN treatment. Determining the mechanism of resistance, whether it is increased responsiveness to IFN,expression of variant genes which impede viral replication, or resistance to viral countermeasures, will uncover modes of HIV resistance relevant to in vivo transmission events.

289 HIV-1-Exposed Seronegative Persons Have Lower Mucosal Innate Immune Reactivity

Jennifer A. Fulcher[1]; Jennifer C. Hoffman[1]; Laura M. Romas[2]; Karen Tanner[1]; Terry Saunders[1]; Julie Elliott[1]; Adam D. Burgener[2]; Peter A. Anton[1]; Otto O. Yang[1]

[1]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US; [2]University of Manitoba, Winnipeg, Canada

Background: Mucosal transmission accounts for the majority of HIV infections, yet is a poorly understood event. Risk of HIV acquisition varies, and there are some individuals who appear to remain uninfected despite repeated high-risk sexual exposures, termed HIV-exposed seronegative (HESN). The immunologic factors contributing to this phenomenon are an area of intense interest. It is known that immune activation and inflammation can facilitate HIV disease progression and transmission. Therefore, we hypothesized that altered immune reactivity may contribute to differences in HIV susceptibility. Since innate immunity serves as the initial defense in mucosal HIV exposure, we have focused our studies on characterizing this response in rectal mucosa, a frequent site of HIV transmission.

Methods: Sigmoid biopsies were obtained from healthy control men (N=12) and from HESN subjects (N=4) identified through the MACS cohort. The biopsies were used in an *ex vivo* mucosal explant model and stimulated with select innate immune ligands (TLR ligands, inactivated whole HIV, HSV-2 and Chlamydia) followed by cytokine expression assays, proteomic studies, gene expression analysis, immunohistochemistry, and HIV infection assays.

Results: Gut mucosal explants from all 16 subjects were susceptible to HIV infection, although there was a trend toward lower replication in HESN subjects. Explants from all subjects produced similar amounts of the non-inflammatory cytokines IL-10, IL-4, and IL-5, both at baseline and in response to innate immune stimuli. As expected, control subject explants also produced large amounts of pro-inflammatory cytokines TNF-α, IL-6, and IL-12. In contrast, no HESN subjects produced detectable levels of these pro-inflammatory

cytokines following stimulation. Proteomic analysis similarly identified several immune response proteins to be differentially expressed between HIV-stimulated HESN and control explants.

Conclusions: Mucosal innate immune reactivity is dampened in HESN subjects as evidenced by absence of pro-inflammatory cytokine production following innate immune stimulation. This may contribute to lower target cell availability leading to lower risk of mucosal HIV transmission in these individuals. Ongoing studies to confirm and characterize these findings will further our understanding of the immunologic events determining HIV susceptibility, thereby providing additional avenues for prevention efforts and microbicide design.

290 Increased Levels of Regulatory T-cells Correlate With Protection From HIV Infection

Laura Pattacini[1]; Jared Baeten[2]; Katherine Thomas[2]; **Tayler Fluharty**[1]; Pamela Murnane[2]; Deborah Donnell[2]; Nelly Mugo[2]; Jairam R. Lingappa[2]; Connie Celum[2]; Jennifer Lund[1]

[1]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [2]University of Washington, Seattle, WA, US

Background: An important challenge related to the development of an HIV vaccine is the lack of known correlates of protection from infection. Individuals who remain seronegative despite repeated HIV exposures (HIV-exposed seronegatives, HESN) offer a relevant model in which to identify correlates of protection. One of the proposed mechanisms of protection from HIV infection is overall immune quiescence, potentially in part due to an increased percentage of regulatory T-cells (Tregs). However, the correlation between Treg frequency and HIV acquisition has not been reported which we investigated in a prospective study of serodiscordant couples.

Methods: Among a cohort of East African subjects highly exposed to HIV as a result of having an HIV-infected partner, we conducted a nested case-control analysis with 142 individuals, who either acquired HIV during follow-up (cases, n=23) or remained HIV uninfected (controls, n=119), selected for highest exposure based on risk score. Samples tested from the cases were the last available peripheral blood mononuclear cells (PBMCs) before the participant became infected. Controls were tested concurrently with cases and those conducting the testing were blinded as to case status. Tregs were identified as CD3+ CD4+ CD25hi CD127lo FoxP3+ cells. Tregs were further characterized by examination of the activation markers CD39, CTLA-4 and ICOS. The frequency of resting and activated Tregs was determined by CD45RA and CD25 expression.

Results: We detected a significantly higher frequency of Tregs in controls, where the average percentage of Tregs among CD3+ T-cells was 3.6%, compared to cases, with 3.1% Tregs (p=0.04). We found no difference in the frequency of resting Tregs (CD45RA+ FoxP3lo), that was 35.2% in controls and 35.0 % in cases (p=0.95) and of activated Tregs, with 4.9% in controls and 5.2% in cases being CD45RA- FoxP3hi (p=0.69). Furthermore, we did not observe any difference in the frequencies of Tregs expressing high levels of the activation markers CD39, CTLA4 and ICOS.

Conclusions: This is the first study to demonstrate a lower Treg frequency in subjects who subsequently seroconverted. Our results support a hypothesis that Tregs could play a protective role against HIV infection.

TUESDAY, FEBRUARY 24, 2015

Session P-C6 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Host Factors in HIV Pathogenesis

291 Estimating the Respective Contributions of Human and Viral Genetic Variation to HIV Control

István Bartha[1]; Paul J. McLaren[1]; Chanson J. Brumme[2]; Richard Harrigan[2]; Amalio Telenti[3]; Jacques Fellay[1]

[1]École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; [2]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; [3]J. Craig Venter Institute, La Jolla, CA, US

Background: Viral load setpoint is a major correlate of HIV disease progression. Genome-wide association studies have identified common human polymorphisms that together explain no more than 15% of its phenotypic variance. Concurrently, studies of the impact of HIV genetic diversity on viral load have produced highly variable estimates. Here we present a joint assessment of the respective contributions of human and viral variation to HIV viral load at setpoint.

Methods: Human genotype data across the Major Histocompatibility Complex (MHC) region, full-length consensus HIV sequences and setpoint viral load results were available for 1034 treatment naïve individuals of European ancestry, infected with HIV-1 subtype B. Heritability (h^2) estimation was carried out with GCTA using three kernel matrices representing: 1) the human Genetic Relatedness Matrix (GRM) derived from the MHC, 2) the viral GRM derived from the full-length sequences, and 3) the sample-specific noise. The human GRM was estimated from 27 common polymorphisms shown to strongly influence viral load selected by LASSO. Bootstrapped phylogenetic trees were inferred from the viral sequences using RAxML. The viral GRM was derived from the phylogenetic trees by taking the branch length of the shared ancestry (i.e. the distance from the root to the most recent common ancestor). The estimates were repeated on 30 bootstrap trees and 15 bootstrap replicates of the samples. Clinical site was included as a covariates in the analyses.

Results: Estimating the host heritability of HIV viral load using the host GRM alone yielded a median estimate of h^2=8% with an interquartile range (IQR) of 1% across 15 bootstrap replicates of the samples. The estimates of the viral heritability drawn from 30 bootstrapped viral trees had a median of 29% (IQR=10%). Combining both the host and viral relatedness matrices showed a comparable viral heritability of 26% (IQR=9%) but a decreased host contribution of 4% (IQR=0%).

Conclusions: This is the first estimate of the combined and respective contributions of the host and the viral genomes to the observed variability of HIV viral load. We showed that both the pathogen and host genomes have detectable impacts on the clinical outcome of infection, which are however not independent. These results suggest that the main predictor of clinical outcome is the viral genotype and that host determination of viral load is largely dependent on its ability to select viral variants.

292 Host Gene Expression Profiles and HIV-1 Infection Outcomes

Romel D. Mackelprang[1]; Ali Filali[2]; Mark Cameron[2]; Rafick P. Sekaly[2]; Elly Katabira[3]; Allan Ronald[4]; Glenda Gray[5]; Connie Celum[1]; M Juliana McElrath[5]; Jairam R. Lingappa[1]

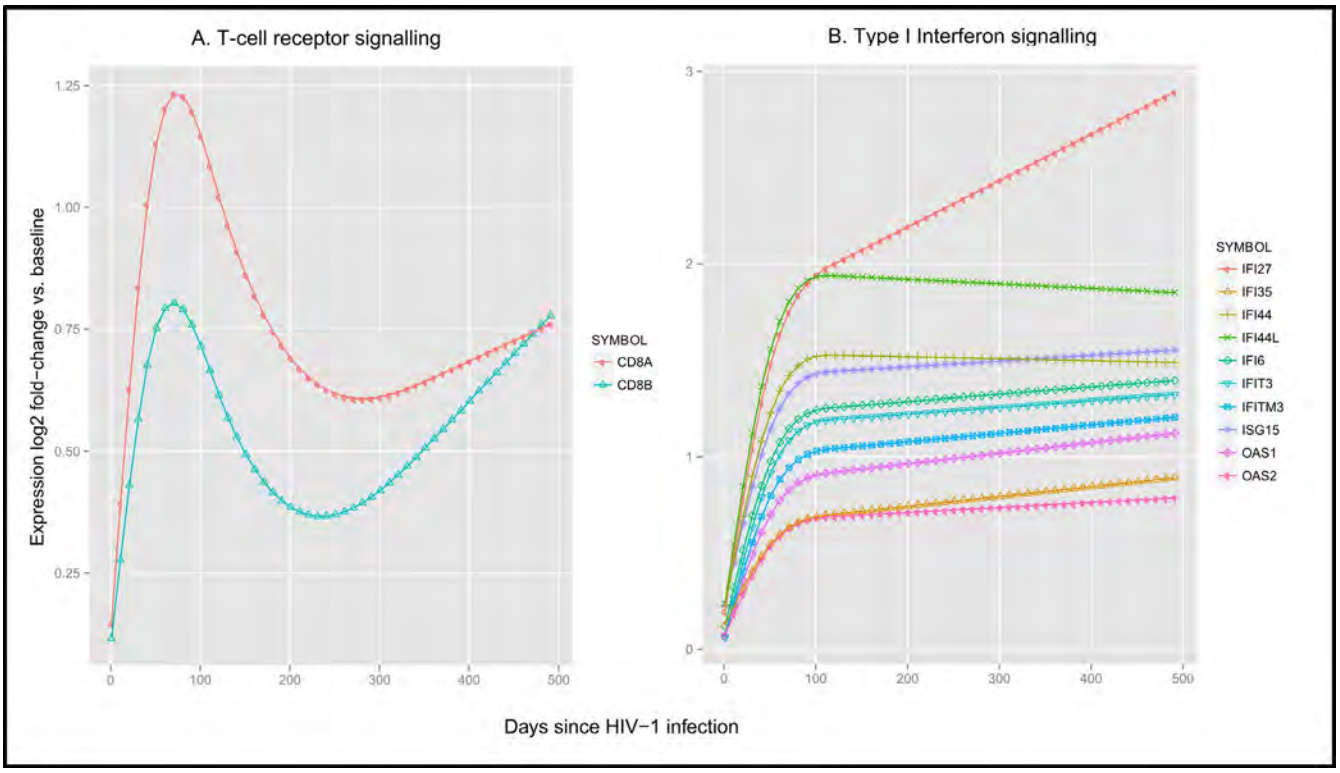
[1]University of Washington, Seattle, WA, US; [2]Case Western Reserve University, Cleveland, OH, US; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]University of Manitoba, Winnipeg, Canada; [5]Fred Hutchinson Cancer Research Center, Seattle, WA, US

Background: HIV-1 infection elicits host gene expression changes that may impact clinical outcomes. Non-human primate studies suggest that early and persistent expression of interferon-stimulated genes differentiate poor outcomes of SIV infection in rhesus macaques from less severe outcomes in sooty mangabeys. We assessed host gene expression in African HIV-1 seroconverters before HIV-1 acquisition through chronic infection to determine if early changes in gene expression associate with subsequent HIV-1 plasma RNA levels and CD4/CD8 ratios.

Methods: Genome-wide gene expression microarrays were performed on 78 whole blood samples from 17 African HIV-1 seroconverters, including 14 pre and 64 post-infection samples (up to 450 days post-infection) collected from HIV-1 serodiscordant heterosexual couples. For each gene, we evaluated expression changes relative to pre-infection

levels using cubic spline linear models to flexibly fit the relationship between expression and time. We used linear regression to determine associations between gene expression changes <90 days after infection with HIV-1 RNA set point and CD4/CD8 ratios >1 year after infection. Ingenuity pathway analysis identified gene sets. P-values were adjusted for multiple testing by controlling the false discovery rate (FDR).

Results: Expression of 1808 genes changed after HIV-1 infection (FDR<5%). Of these, the maximum expected fold-change during follow-up was 1.4-2 for 408 genes, and >2 for 35 genes. Within 90 days after HIV-1 infection, expression of 7 genes involved in T-cell receptor signaling (e.g. CD8a and CD8b) increased nearly 2-fold versus pre-infection levels before subsequently declining (p=0.03)(Figure 1a). Expression of 28 genes involved in the Type I interferon (IFN) pathway (e.g., IFI27, IFI44, MX1, Tetherin, OAS1/2) increased rapidly <90 days after infection and remained elevated throughout follow-up ($p=9.7x10^{-10}$,FDR<5%)(Figure 1b). IFI27 expression increased most with a 4-fold increase by 90 days after infection (p=0.0007,FDR=2%). Increased expression of genes in the Type I IFN pathway <90 days after infection was associated with increased CD4/CD8 ratios ($p=2x10^{-7}$,FDR<5%), but not HIV-1 set point.



Temporal trajectories of representative genes involved in T-cell receptor signaling (A) and Type I inferferon responses (B). Trajectories were determined using cubic spline linear models to allow flexible relationships between time since HIV-1 infection and gene expression changes. Post-infection gene expression values were evaluated relative to pre-infection values to allow analysis of within-person changes in gene expression.

Conclusions: Similar to rhesus macaques, Type I IFN stimulated genes are persistently expressed during early HIV-1 infection. Expression of these genes is associated with CD4/CD8 ratio but not HIV-1 set point. Further research is needed to identify mechanisms for how ISG expression may alter clinical outcomes.

293 Refinement of Association Signals Assessment of Residual Heritability in Host Control of HIV Viral Load

Paul J. McLaren; **Istvan Bartha**; Jacques Fellay
École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

Background: Genome-wide association studies of HIV outcome consistently identify the MHC region as the major genetic influence on disease progression. Through establishment of the International Collaboration for the Genomics of HIV we sought to bring together all existing GWAS data in HIV patients to maximize power to uncover further association signals.

Methods: Genome-wide SNP data were collected from 25 clinical centers. Plasma viral load measurements obtained during the chronic phase of untreated infection were available for 6,315 individuals of European ancestry. Missing genotypes were imputed using the 1,000 Genomes Project reference. Single marker association testing was performed per study using linear regression and combined across studies by meta-analysis. Classical HLA alleles and amino acid variants were imputed using the SNP2HLA pipeline. Heritability estimates were calculated using GCTA.

Results: Consistent with previous studies, the top association signal was amino acid position 97 in HLA-B (p=4e-143), with independent associations at positions 67 (p=4e-112) and 45 (p=8e-49) in HLA-B and positions 77 (p=2e-12) and 95 (p=4e-5) in HLA-A. All 5 amino acid positions are located in the peptide-binding groove. Controlling for these positions fully accounted for classical class I HLA allele associations. Independent of the MHC, a second peak of association in the CCR5 region (top SNP rs4317138 p=8e-19) was observed. Conditioning out the known effect of CCR5Δ32, 57 SNPs remained associated at genome-wide significance (p<5e-8) suggesting multiple additional causal variants in this region. Considering all SNPs and assuming an additive genetic model, we obtained a narrow-sense heritability (h2) estimate of 26% (p<2e-16) for viral load. Removing the HLA and CCR5 regions, we observed a reduced, yet still significant h2 estimate of 16% (p=5e-8).

Conclusions: By combining available GWAS data in HIV infected individuals we refined the known association signals in HLA class I and CCR5. Controlling for these main effects, we uncovered additional, independent associations in known regions. Heritability analysis suggested that variation outside known regions, captured through common SNPs, also contribute to HIV control.

294 Genetic and Clinical Predictors of CD4 Recovery During Suppressive cART: WIHS

Ruth M. Greenblatt[1]; Kord Kober[1]; Peter Bacchetti[1]; Ross Boylan[1]; Kathryn Anastos[2]; Mardge Cohen[5]; Mary A. Young[3]; Deborah Gustafson[4]; Bradley Aouizerat[1]
On behalf of the WIHS

[1]University of California San Francisco, San Francisco, CA, US; [2]Montefiore Medical Center, University Hospital for Albert Einstein College of Medicine, New York, NY, US; [3]Georgetown University, Washington, DC, US; [4]State University of New York, Downstate, Brooklyn, NY, US; [5]CORE Center, Chicago, IL, US; [6]National Institutes of Health (NIH), Bethesda, MD, US

Background: Blood CD4 cell counts fail to recover in a significant minority of virologically suppressed cART recipients. We hypothesized that host genetics, including novel mutations, and key clinical characteristics would predict rapid versus slow recovery in women with HIV RNA levels below detection during cART.

Methods: Longitudinal treatment response and clinical data were generated by the WIHS cohort, and used to define rapid vs. slow CD4 cell recovery among women during, at a minimum, the first 2.5 years of cART with virologic suppression. Whole exome sequencing (WES) was conducted on 95 women, with the most consistently slow (n=47) or rapid (n=48) CD4 recoveries. Additive stepwise logistic regression identified statistically significant predictors of rapid recovery.

Results: Each decade increase in age at the start of viral suppression while on cART reduced the odds ratio (OR) of rapid recovery by 0.50 (95% CI 0.27-0.92). Self-reported adherence ≥95% increased the OR of rapid recovery by 2.7 (CI 1.04-7.0). When added as a third predictor, higher CD4 nadir approached statistical significance (OR 1.34 per 100 cells, CI 0.96-1.87). Following WES analysis, rapid CD4 recovery was statistically significantly associated with sequence anomalies aggregated at the gene level for 68 genes (all p<0.001). Notably, the host genes identified were enriched for genes (n=14; 20.6%) that encode for proteins that interact with HIV-encoded proteins. An additional 38 genes (55.9%) encode for proteins that in turn interact with other host proteins known to interact with HIV-encoded proteins.

Conclusions: Despite consistent viral loads below detection on cART, self-reported nonadherence and higher age adversely influenced CD4 recovery. The finding that nonadherence and polymorphisms of HIV target genes influence CD4 recovery suggest that intermittent or low grade viral replication contributed to slow CD4 response in this sample of cART recipients with ≥2.5 years of virologic suppression.

295 Host Genetic Predictors of Plasma Kynurenine/Tryptophan Among Treated HIV+ Ugandans

Sulggi A. Lee[1]; Joel Mefford[1]; Yong Huang[1]; John S. Witte[1]; Jeffrey Martin[1]; David R. Bangsberg[2]; Taisei Mushiroda[3]; Michiaki Kubo[3]; Deanna Kroetz[1]; Peter W. Hunt[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Massachusetts General Hospital and Harvard University, Boston, MA, US; [3]RIKEN Center for Genomic Medicine, Wako, Japan

Background: Indoleamine 2,3-dioxygenase-1 (IDO) activity, as assessed by plasma kynurenine/tryptophan (KT) ratio, is induced by immune activation and microbial translocation, causes T cell proliferative defects and Th17 depletion, and strongly predicts mortality in treated HIV infection. Whether host genetic variation contributes to IDO activity is unknown.

Methods: We assessed common genetic polymorphisms in association with plasma KT ratio in HIV-infected Ugandans in the UARTO and ARKS cohorts at months 6 and 12 of confirmed antiretroviral therapy (ART)-mediated viral suppression using genome (Illumina OmniExpress) and exome (Affymetrix Axiom) array genotyping. Linear mixed models adjusted for cohort, gender, pregnancy status, and population ancestry were employed for candidate gene and discovery-based analyses. Genome-wide imputation was performed using the 1000 Genomes reference panel. For the candidate gene analysis, genes encoding known factors that induce IDO were included.

Results: Participants (N=597) were mostly female (62%) with a median age of 35, and had advanced disease (median pre-ART CD4+ count 135 cells/mm^3 and HIV RNA 5.1 $\log_{10}$copies/mL). For the candidate gene analysis, single nucleotide polymorphisms (SNPs) in *TNF* (rs17200810[a], rs34451538, rs114064880, rs11575838), *IFNGR1* (rs276565[a]), and *TLR4* (rs2770148[b]) genes were significant at Bonferroni *P* <5E10-5. For the GWAS analysis, one intergenic SNP (between *CSPG5* and *ELP6*) achieved genomewide significance (rs56185965, *P*=8.7E-09), while several other SNPs achieved near-genomewide significance at *P* <5E10-7, including genes encoding 2 different protein tyrosine phosphatases involved in reversible phosphorylation during cell signaling, *PTPRM* (rs75257475[b], rs115059620) and *PTPRN2* (rs6950107), as well as a SNP downstream of *CYP24A1* (rs13041834[b]), which encodes an enzyme that plays a major role in vitamin D metabolism and lies in an H3K27Ac histone mark-enriched region.

Conclusions: Our candidate gene analysis suggests that host genetic variation may modify the impact of IFN-g, TNF-a, and microbial products (via toll-like receptor 4) on IDO induction. The GWAS analysis also identified potential novel mechanisms by which host genetics may modify IDO induction via protein tyrosine phosphatase or vitamin D pathways. Additional studies are needed to confirm these findings in other populations and to validate their functional impact on IDO induction.

[a] Genotyped SNP; [b] In linkage disequilibrium (LD) with a genotyped SNP

296 Regulation of IL-32 Expression by a Promoter Polymorphism and MicroRNA29b in HIV-1 Patients

Carolina Scagnolari; Giulia Cacciotti; Carla Selvaggi; Noemi Giustini; Ivano Mezzaroma; Massimo Gentile; Gabriella D'Ettorre; Ombretta Turrziani; Vincenzo Vullo; Guido Antonelli

Sapienza University of Rome, Rome, Italy

Background: Interleukin-32 (IL-32) is a multi-isoform cytokine that has recently received growing attention as a key component in the antiviral immune response to HIV-1 infection. We previously demonstrated that IL-32 isoforms are highly expressed during HIV-1 infection and that it is associated with low levels of viremia and can increase the expression of well-established type I IFN induced mixovirus resistance proteins A (MxA). Now, we evaluated whether changes in miRNA-29b levels, which has been shown to target the IL-32 mRNA 3'-untranslated region, and a promoter polymorphism in the IL-32 gene, influence IL-32 isoforms and indirectly MxA expression in untreated HIV-1 infected patients

Methods: PBMC samples from 104 untreated HIV-1 infected patients (male/female 82/22; median age: 40 years; median viral load: 46580 HIV-RNA copies/ml and median CD4+T cell count: 355 cells/mm^3) were collected at the Sapienza University Hospital (Rome, Italy). Levels of IL-32 isoforms (α and nonα) mRNA, MxA-mRNA, microRNA29b and rs28372698 (T/A) IL-32 promoter single nucleotide polymorphisms (SNPs) were evaluated by using distinct TaqMan *assays*.

Results: The IL-32 rs28372698 (T/A) genotype frequency was TT (26 %), AT (53%) and AA (21%) among untreated HIV-1 infected patients. We found that patients carrying AA IL-32 genotype have higher expression of IL-32 isoforms (α and nonα) and MxA than those with AT or TT IL-32 genotypes concomitantly with a twofold decrease on HIV-1 viral load. No differences in terms of CD4+ T cell counts were recorded among HIV-1 infected patients carrying different IL-32 genotypes. Furthermore, an inverse correlation between miR-29b and IL-32nonα levels was observed in HIV positive patients ($p<0.05$; r=-0.27) while no significant correlation was found with IL-32α levels. Lastly we found that a strong positive correlation between IL-32nonα and MxA transcript levels exists (p<0.001; r=0.58) and that patients expressing higher levels of miR-29b showed lower levels of MxA (p<0.01; r=-0.41).

Conclusions: Our results indicate that the expression of anti HIV-1 IL-32 isoforms are influenced both by the presence of IL32 promoter polymorphism and levels of miRNA-29b, highlighting the importance of host genetic factors and cellular microRNA in the regulation of IL-32 during HIV-1 patients.

297 LILRA3 Deletion Is a Genetic Risk Factor of HIV Infection

Gerrit Ahrenstorf[1]; Hui Zhi Low[1]; Katja kniesch[1]; Matthias Stoll[1]; Dirk Meyer-Olson[1]; Torsten Matthias[2]; Reinhold E. Schmidt[1]; Torsten Witte[1]

[1]Hannover Medical School, Hannover, Germany; [2]AESKU Diagnostics, Wendelsheim, Germany

Background: Both the risk of transmission of HIV and the clinical course of the disease are influenced by viral pathogenicity as well as host factors. LILRA3 a protein of the leukocyte immunoglobulin-like receptor family exerts various immunmodulatory functions. A naturally occuring 6.7 kbp deletion in the gene locus of LILRA3 results in a null allele and an absence of the protein. The influence of LILRA3 and of the genetic LILRA3 deletion on the transmission and the clinical course of HIV infection was analyzed in this study.

Methods: LILRA3 genotypes were determined by polymerase chain reaction. HIV infected patients that were followed for at least 24 months were categorized into short-term progressors, normal progressors and long-term non-progressors according to the clinical and immunological course. Studies of LILRA3 gene regulation and protein concentrations were performed using real-time PCR, intracellular flow cytometry and ELISA.

Results: The prevalence of homozygous LILRA3 deletion was significantly higher in HIV positive individuals (n= 415) than in controls (n= 615) (p= 0.02). The progression of the disease was faster in patients with homozygous LILRA3 deletion with a higher proportion of short-term progressors among homozygously deleted patients than in heterozygous (p= 0.03) and in homozygously positive (p=0.002) individuals. The relative risk for a faster progression was 1.5 times higher in heterozygous individuals and 3 times in homozygously LILRA3 negative individuals when compared to homozygously positive ones. Functional analysis revealed an upregulation of the LILRA3 gene in Real-time PCR in treated HIV patients when compared to untreated patients (p= 0.007) and controls (p= 0.02) resulting in a higher LILRA3 expression in $CD4^+$ (p= 0.008) and $CD14^+$ (p= 0.02) cells of untreated patients than in controls in intracellular flow cytometry. LILRA3 concentrations in the sera were similar between the groups, in untreated patients a correlation between viral load and LILRA3 concentration was found.

Conclusions: The homozygous LILRA3 deletion is associated with a higher susceptibility for HIV disease and with a faster disease progression in HIV infected individuals.

298LB SIV Infection Triggers Endothelial Dysfunction and Diminished Expression of Krüppel-Like Factor 2 (KLF2) in Nonhuman Primates

Soumya Panigrahi[1]; Michael L. Freeman[1]; joseph C. mudd[4]; Nicholas Funderburg[2]; Scott Sieg[1]; David A. Zidar[1]; Mirko Paiardini[3]; Francois Villinger[3]; Mukesh K. Jain[1]; michael lederman[1]

[1]Case Western Reserve University/University Hospitals Medical Center, Cleveland, OH, US; [2]Ohio State University School of Health and Rehabilitation Sciences, Columbus, OH, US; [3]Emory University, Atlanta, GA, US; [4]Lab of Molecular Microbiology, Bethesda, MD, US

Background: Life-saving, long-term anti-retroviral therapy (ART) is linked to increased risk of thromboembolism and cardiovascular co-morbidities. While immune activation, bacterial translocation, oxidative stress, and chronic vascular inflammation are the prime predicted triggering factors, a through mechanistic knowledge is still lacking. Here, we examined endothelium of SIV infected Rhesus macaque with the hypothesis that key markers of endothelial dysfunction and expression of Krüppel-like factor 2 (KLF2), a transcriptional master regulator of an anti-thrombotic endothelial environment, will be modulated.

Methods: Sections of paraffin-embedded thorasic aorta from SIV (SHIVSF162P3) infected and uninfected *Rhesus macaques* were used in this study. H&E staining to identify any morphological alteration or sub-endothelial infiltration of inflammatory cells and immunohistochemistry methods were applied to detect endothelial eNOS and KLF2 expression by epi-fluorescent microscopy (EVOS®FL). Public domain software ImageJ v1.38e was used for the digital image data analysis. We also investigated the *in vitro* effect of statin on KLF2 expression in human aortic endothelial cells.

Results: Focal endothelial proliferation, and sub-endothelial infiltrations at multiple sites were found in H&E stained sections of 3 out of 4 infected animals, compared to none in the 22 controls. This observation was further refined by immune-fluorescence detection of sub-endothelial monocytes (CD68+), T lymphocytes (CD8+), and platelets (CD41+) in the infected group. We observed significant reduction ($p < 0.001$) of eNOS expression in all 4 infected animals (Fig 1a). We also detected significantly lower ($p < 0.0001$) KLF2 expression in the endothelium of the infected animals (Fig 1b). Moreover, our results indicate that simvastatin protects human aortic endothelial cells from LPS and oxLDL induced down-regulation of KLF2.

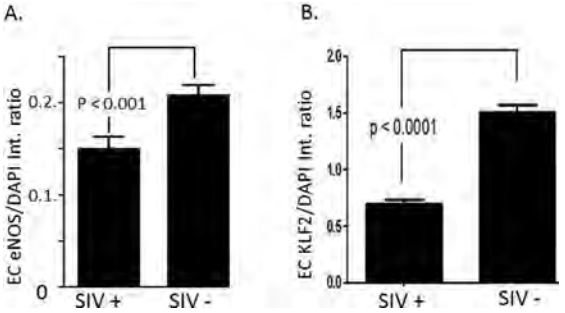


Figure1. *Endothelial Dysfunction and reduced Krüppel-like Factor expression in SIV infection:* A. Endothelial eNOS B. Endothelial KLF2 (cumulative data from 100 endothelial cells in each aortic section of 4 infected and 4 control animals).

Conclusions: Here we show for the first time direct evidence that SIV infected Rhesus macaques have dysfunctional vascular endothelium with sub-endothelial infiltration of inflammatory cells indicating early atherosclerotic changes. We also report for the first time a significant down-regulation of endothelial KLF2 in SIV infected animals. In addition, while lipid dysregulation and bacterial translocation may prime the initiation and maintenance of a pro-thrombotic endothelium in HIV infection, our *in vitro* data indicate that statin can protect endothelial cells from LPS and oxLDL induced KLF2 down-regulation.

299LB A Novel Method Using ^2H_2O to Measure Collagen Turnover in HIV-Infected Individuals

Leslie R. Cockerham[1]; Claire Emson[2]; Ma Somsouk[1]; Kara Harvill[1]; Kevin Li[2]; Scott M. Turner[2]; Martin L. Decaris[2]; Marc K. Hellerstein[3]; Steven G. Deeks[1]; Hiroyu Hatano[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]KineMed, Inc, Emeryville, CA, US; [3]University of California Berkeley, Berkeley, CA, US

Background: Lymphoid tissue fibrosis occurs early in HIV infection and is thought to be a central factor in the pathogenesis of HIV by impairing T cell homeostasis. Collagen deposition is a dynamic process, and traditional histologic techniques cannot distinguish between new collagen deposition and any fibrosis that may have accumulated during the untreated phase of HIV infection. We investigated the use of a technique utilizing ^2H_2O (heavy water) intake to quantify new collagen deposition in gut-associated lymphoid tissue (GALT) in treated HIV-infected individuals.

Methods: Eighteen HIV-infected individuals on suppressive ART received outpatient oral doses of ^2H_2O for 4 weeks and underwent colorectal biopsies. ^2H_2O enrichment in total body water (TBW) in each patient was quantified from weekly salivary swabs during ^2H_2O administration. Single 3mm biopsy pieces were subjected to sequential physical and

chemical extraction methods to fractionate collagen molecules based on solubility in guanidine HCl. Guanidine-soluble collagen represents more recently synthesized, less cross-linked collagen. Incorporation of the ^2H_2O tracer into collagen in GALT was quantified by liquid-chromatography-mass spectrometry and fractional synthesis rate (FSR; per week) was calculated for guanidine-soluble and -insoluble GALT collagen.

Results: Outpatient administration of ^2H_2O was well tolerated. After 28 days of ^2H_2O intake, subjects reached the target goal of 1-2% ^2H_2O enrichment in TBW. The median FSR of guanidine-insoluble collagen in GALT was 3.2% per week (IQR 2.9%-3.9%). Guanidine-soluble collagen in GALT turned over much more quickly, with a median FSR of 12.8% per week (IQR 12.3%-16.1%). In comparison with other human studies where collagen FSR was measured by ^2H_2O labeling, the FSRs in GALT were 5-fold higher than the FSRs of skin collagen in healthy volunteers but similar to the FSR of liver collagen in patients with fibrotic liver disease.

Conclusions: The relatively high rates of collagen turnover observed in the GALT during treated HIV disease (guanidine soluble collagen half-life ~ 5 weeks) suggest that collagen deposition and turnover is ongoing and dynamic in this setting, and may therefore be amenable to interventions. The ^2H_2O labeling technique provides an assessment of collagen turnover rates, in contrast to static metrics from traditional histologic techniques, and may be useful for evaluating the effects of future anti-fibrotic therapies.

THURSDAY, FEBRUARY 26, 2015

Session P-C7 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HIV/CMV Interactions in Transmission and Pathogenesis

300 Effect of CMV and HIV Replication on T-Cell Exhaustion and Senescence During ART

Jennifer M. Dan[1]; Marta Massanella[1]; David M. Smith[1]; Eric S. Daar[2]; Michael P. Dube[3]; Richard Haubrich[1]; Sheldon Morris[1]; Sara Gianella Weibel[1]

[1]University of California San Diego, La Jolla, CA, US; [2]Harbor–University of California Los Angeles Medical Center, Torrance, CA, US; [3]University of Southern California Keck School of Medicine, Los Angeles, CA, US

Background: HIV-infected men who have sex with men (MSM) are nearly universally infected with CMV, and both viruses are associated with T-cell dysfunction and inflammation-related morbidities. The effect of asymptomatic CMV replication and persistent HIV transcription during suppressive ART on markers of T cell exhaustion and senescence is poorly defined.

Methods: Paired seminal and blood samples from 45 asymptomatic chronically HIV-infected CMV-seropositive MSM on long term ART and with HIV RNA levels in blood plasma <50 copies/ml were studied. Levels of CMV DNA in semen and blood were measured by RT-PCR, and cell-associated HIV DNA and RNA transcripts (unspliced) were measured in PBMC by droplet digital PCR. Markers of T cell exhaustion (PD-1) and senescence (CD57) were measured in PBMC by flow cytometry for CD4 and CD8 T cells and subsets (naïve [$CD45RA^+CD27^+CD28^+$], central memory [$CD45RA^-CD27^+CD28^+$], effectors [$CD4^+CD45RA^{-/+}CD27^-CD28^+$ or $CD8^+CD45RA^{-/+}CD27^+CD28^-$] and terminally differentiated [$CD45RA^{+/-}CD27^-CD28^-$]). Associations between immunological markers and asymptomatic CMV and HIV replication, HIV DNA, CMV IgG, age, current and nadir CD4 and time on ART were determined using univariate and multivariate analysis.

Results: CMV DNA was detected in 42% of seminal samples and 20% of PBMC. Detectable CMV DNA in semen but not blood was associated with increased PD-1 expression on circulating CD4 T cells compared to no CMV (P=0.01), particularly in the effector and terminally differentiated subsets (P<0.05). Similarly, higher levels of cellular HIV RNA (but not HIV DNA) were positively associated with greater PD-1 expression on total CD4 and central memory blood subset (P<0.01). There was no association between CMV DNA (blood and semen) or cellular HIV RNA with CD8 exhaustion or senescence or with markers of CD4 senescence. In multivariate analysis, detection of seminal CMV and higher cellular HIV RNA remained associated with increased PD-1 expression on total CD4 T cells (P<0.05). No other variable contributed significantly to the model.

Conclusions: Our data suggest that detection of CMV in the genital tract may contribute to the activation of the PD-1 axis on circulating T cells during suppressive ART. Because increased PD-1 on T cells has been implicated in the maintenance of the HIV reservoir, HIV disease progression and the inability of the immune system to adequately control HIV infection, future studies should examine whether CMV-dependent mechanisms play a role in T cell exhaustion.

301 HIV Myeloid Derived Suppressor Cells Control Cytomegalovirus Inflammation by IL-27

Ankita Garg; Stephen Spector

University of California San Diego, La Jolla, CA, US

Background: CMV is associated with persistent inflammation in HIV-infected persons. Here, we studied the effect of HIV expanded myeloid derived suppressor cells (MDSCs) in controlling CMV specific inflammation.

Methods: PBMCs from HIV–/CMV-seropositive (CMV+) donors were cultured in presence of heat inactivated HIV. After 5 days, $CD11b^+CD33^+CD14^+HLA\ DR^{hi}$ (DR^{hi} monocytes) and $CD11b^+CD33^+CD14^+HLA\ DR^{-/lo}$ (MDSCs) cell subsets were sorted by flow cytometry. B7H4 (a negative regulator of T cell function) was silenced using siRNA and cultured with/without autologous PBMCs in presence/absence of CMV pp65 peptides (pp65; 1μg/ml). In some experiments, PBMCs were cultured with HIV/pp65 in presence/absence of neutralizing anti-IL-27 antibody. Enumeration of B7H4 on MDSCs, regulatory T-cells, intracellular IFNγ, activated forms phospho(p)-Zap70 and p-Akt were determined by flow cytometry; IFNγ and IL-27 were quantified by ELISA. Data were analyzed using two-tailed, paired Student's *t* test.

Results: MDSCs cultured with autologous PBMCs exposed to pp65 caused a decrease in IFNγ production vs. controls or DR^{hi} monocytes (p=0.002). IFNγ release was restored when MDSCs were transfected with B7H4 siRNA and cultured with PBMCs in presence of pp65 (p=0.02). MDSCs cultured with PBMCs did not alter pp65 induced activation of proximal T-cell signaling molecule Zap70 but decreased activation of Akt; this was restored when B7H4 was knocked down in MDSCs cultured with PBMCs. Culture of MDSCs with pp65 produced more IL-27 vs. control MDSCs and DR^{hi} monocytes (p=0.05). Culture of CMV+ PBMCs with pp65 increased the frequency of $CD4^+IFN\gamma^+$ cells and release of IFNγ in supernatants vs. controls (p=0.04). IFNγ was further increased when PBMCs were cultured in presence of anti-IL-27 and stimulated with pp65; CMV– PBMCs did not produce IFNγ when treated with pp65. Furthermore, culture of CMV+ PBMCs with pp65 led to expansion of $FoxP3^+$ Tregs vs. controls (p=0.02) and CMV– (p=0.003); addition of anti-IL-27 had no effect on Treg expansion. Finally, HIV expanded MDSCs had increased expression of B7H4 when compared to DR^{hi} monocytes (p=0.03) which was inhibited in the presence of anti-IL-27 neutralizing antibody (p=0.05).

Conclusions: These findings suggest that IL-27 down regulates IFNγ during CMV infection. IL-27 induces B7H4 expression on HIV MDSCs which controls CMV induced T-cell IFNγ production by inhibiting p-Akt. IL-27 and B7H4 provide new therapeutic targets to control inflammation during HIV infection.

302 Persistent Elevation of Inflammation Markers in HIV+ Persons With CMV Disease

Melissa Schechter[1]; Bruno Andrade[2]; Eleanor M. Wilson[1]; Virginia Sheikh[2]; Sonya Krishnan[2]; Margaret Caplan[1]; Gregg Roby[2]; Adam Rupert[3]; Peter Burbelo[4]; Irini Sereti[2]

[1]NIAID, Leidos Biomedical Inc., Fredrick, MD, US; [2]National Institute of Allergy and Infectious Diseases, Bethesda, MD, US; [3]NIAID, Leidos Biomedical Inc., Fredrick, MD, US; [4]National Institute of Dental and Craniofacial Research, Bethesda, MD, US

Background: HIV+ individuals have a high prevalence of cytomegalovirus (CMV) co-infection and a minority of them develop CMV-associated end organ disease (EOD). CMV co-infection has also been associated with increased risk for cardiovascular events. The potential contribution of CMV infection or disease in chronic immune activation and non-infectious complications in HIV remains unclear.

Methods: In a case control study, HIV+ persons (CD4 <100 cells/μL pre-ART) with CMV EOD (N=25) or detectable CMV viremia (N=7) pre-ART were matched 1:1 by CD4 T-cell counts and age with HIV+ persons with undetectable CMV viremia by PCR. Participants were evaluated pre-ART (week 0) and at week (W) 12 and 48 after ART initiation. Cryopreserved plasma was used to measure markers of inflammation (CRP, IFN-γ, IL-12 p70, IL-10, IL-1β, IL-8, IL-6, TNF-α), monocyte activation and vascular injury (sICAM-3, E-Selectin, sCD14, sTF, MP-TF, CX3CL1, P-Selectin, Thrombomodulin, SAA, MCP-1, Eotaxin-3) and coagulation (D-dimer, Factor X Chromogenic, TF Chromogenic) by ELISA-based assays. Data were analyzed using Mann-Whitney and Spearman rank (correlation) tests.

Results: EOD cases were 66% male, with median age of 41 years, CD4 of 11 cells/μL, plasma HIV RNA of 5.12 $\log_{10}$ c/mL and CMV PCR 2.93 $\log_{10}$ c/mL units at W0. EOD cases had higher plasma levels of HIV RNA (p=0.01), CRP (p=0.03), IFN-γ (p=0.02), IL-10 (p=0.01), IL-8 (p=0.01), IL-6 (p=0.03), and SAA (p=0.001) compared to controls at W0. At W12, SAA (p=0.02), IFN-γ (p=0.0002), IL-10 (p=0.0003), IL-8 (p=0.01) and TNF-α (p=0.003) remained higher in EOD cases than in controls. At W48, IFN-γ (p=0.0.01), TNF-α (p=0.02) and IL-12 p70 (p=0.04) were persistently higher in EOD cases than in controls. Baseline, CMV IgG levels inversely correlated with sCD14 (r=-0.3, p=0.04), Fractalkine (r=-0.3, p=0.02) and HIV viral load (r=-0.33, p=0.01) but not with presence of EOD.

Conclusions: CMV end organ disease and viremia in HIV+ persons is associated with increased plasma levels of inflammatory and vascular injury biomarkers pre-ART with some persisting after ART. Our data suggest a protracted inflammatory response to CMV that may contribute to HIV pathogenesis and non-infectious complications.

Funded by NCI Contract No. HHSN261200800001E. This research was supported [in part] by the National Institute of Allergy and Infectious Diseases.

303 sCD163 Increase in HIV/CMV-Coinfected Subjects Included in ICONA Cohort

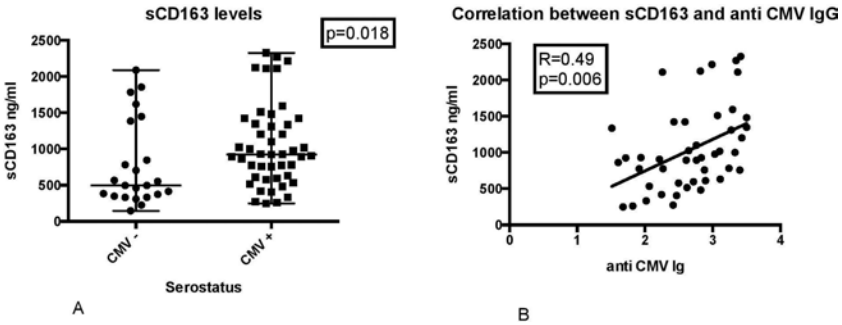
Serena Vita[3]; Miriam Lichtner[1]; Giulia Marchetti[2]; Claudia Mascia[3]; Esther Merlini[2]; Paola Cicconi[2]; Vincenzo Vullo[3]; Pier Luigi Viale[5]; Alberto Costantini[4]; Antonella d'Arminio Monforte[2]
For the Icona Foundation Study

[1]University of Rome La Sapienza, Polo Pontino, Latina, Italy; [2]San Paolo Hospital, Milano, Italy; [3]University of Rome La Sapienza, Rome, Italy; [4]University of Ancona, Ancona, Italy; [5]University of Bologna, Bologna, Italy

Background: Accumulating evidence suggest that inflammatory cytokines produced by monocytes/macrophages play a role in the vascular disease and cognitive decline**.** In HIV patients, herpes virus coinfection has been proposed as a key factor in sustaining immune activation, even in presence of HIV plasma viral control. In our previous study on the ICONA cohort we showed that in HIV patients (pts), CMV infection is an independent risk factor for non AIDS events/deaths.

Methods: We screened all the ICONA pts with an available CMV serology at enrolment (<= 6 months) and a plasma sample after ≥1 year of successful ART (defined as an undetectable HIV viral load and CD4+ count >200/mc). Pts were grouped according to CMV serostatus in CMV-infected (CMV+) (defined as CMV IgG positive) and CMV-uninfected (CMV-). Pts were also matched 2:1 for the following parameters: age, CD4 nadir, duration of HIV infection, HBV and HCV. We excluded pts with previous or current CMV organ diseases and other active organ disease in the previous 5 years. We detected sCD163, TNFα, sCD14, IL-6 using ELISA tests (R&D Systems) on plasma samples. All sample were retested for anti-CMV IgG (GenWay Biotech). Statistical analysis was performed using Mann-Withney Test and Spearman correlation analysis.

Results: A total of 69 subjects were recruited, 46 HIV monoinfected (CMV-) and 23 HIV/CMV (CMV+) coinfected. A higher median of sCD163 level (927.7 vs. 497.8 ng/ml, p=0.018) was found in CMV+ compared to CMV- group. TNFα, sCD14 were also elevated but didn't reach a significant difference in comparison to HIV/CMV- subjects. In HIV/CMV+ subjects a significant correlation was shown between anti-CMV IgG levels and sCD163 (r=0.49, p=0.006) (Fig.1). Moreover only in CMV+ subjects sCD163 levels were related to the duration of HIV infection (r=0.29, p=0.04). In the CMV positive group comparing CMV IgG levels with CD4 count, at the time of sampling, we found a significant negative correlation (r=0.39, p=0.0006).



Conclusions: CMV chronic infection appears to be linked to an increase in sCD163, a markers of myeloid activation, in HIV infected subjects under successful ART with controlled biological (age and sex) and HIV related (HIV suppression, CD4 nadir and CD4 recovery) factors. The persistent activation of monocytes and macrophages that has been implicated in the accelerated development of vascular and neurological disease in general population, may explain the increased risk of non AIDS events found in CMV/HIV coinfected subjects.

304 Genital CMV Shedding Predicts Syphilis Acquisition in HIV-Infected MSM on ART

Sara Gianella Weibel[1]; David M. Smith[1]; Eric Daar[2]; Michael Dube[3]; Andrea Lisco[4]; Christophe Vanpouille[5]; Richard Haubrich[1]; Sheldon Morris[1]

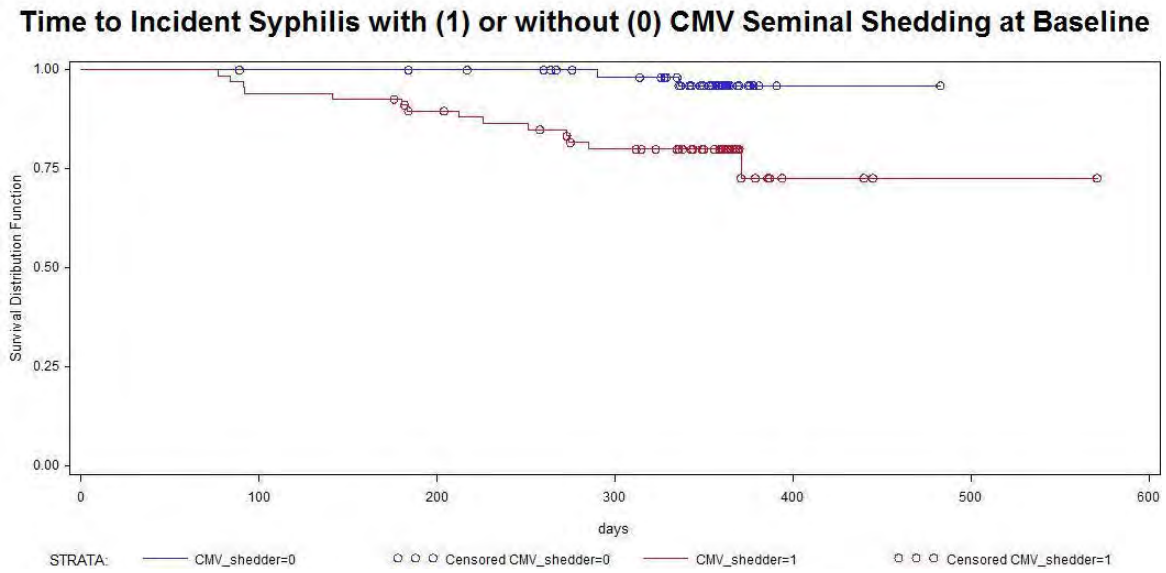
[1]University of California San Diego, La Jolla, CA, US; [2]Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, CA, US; [3]University of Southern California Keck School of Medicine, Los Angeles, CA, US; [4]National Institute of Allergy and Infectious Diseases, Bethesda, MD, US; [5]National Institute of Child Health and Human Development, Bethesda, MD, US

Background: Bacterial sexually transmitted infections (STI) are highly prevalent among HIV-infected men who have sex with men (MSM) and are co-factors in HIV transmission. While sexual behavior and networks are important in STI acquisition, other biological factors have not been emphasized as targets for intervention.

Methods: As part of a behavioral intervention, 136 HIV-infected MSM on suppressive (<500 copies/ml) ART were followed for 12 months and screened for incident bacterial STI (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and syphilis*)* every three months. Baseline predictors of bacterial STI were determined using survival analysis of time to incident

STI. Tested variables at baseline included: behavioral factors (number of sex partners, number of anal sex acts, use of methamphetamine and other drugs), plasma HIV RNA levels, current and nadir CD4 T and CD8 T cell count, genital shedding of herpes viruses (CMV, EBV, HSV, HHV-6, -7, and -8), serum CMV IgG levels, and soluble markers of genital inflammation (MCP-1, IL-6, TNF-alfa, Interferon-gamma, RANTES and IP-10 in baseline seminal plasma).

Results: Thirty-four subjects (26.2%) acquired bacterial STIs during follow-up, sometimes with more than one pathogen (16 syphilis, 20 gonorrhea, 14 chlamydia). Acquisition of syphilis during follow-up was associated with genital CMV shedding at baseline (21% in CMV shedders versus 3% in non-shedders, P=0.003, see figure attached), younger age (P=0.005) and more sex partners (P=0.047). None of the tested variables except partner number was associated with acquisition of other STIs (chlamydia and gonorrhea at any site). For the acquisition of syphilis, in multivariable Cox-proportional hazard model adjusted hazard rates were as follows: baseline CMV shedding 4.87 (95% CI 1.06-22.47), age 0.96 (per year younger [95% 0.91-1.01]) and number of partners past month 1.06 (per partner per month [0.99-1.13]). Also, syphilis cases compared to non-cases had lower baseline levels of seminal MCP-1 (P=0.01), and lower seminal MCP-1 levels were associated with higher levels of seminal CMV DNA (P=0.005).



Kaplan-Meier Plot showing incidence of Syphilis acquisition in participant with (1) and without (0) CMV seminal shedding at baseline.

Conclusions: In this prospective study, presence of genital CMV shedding at baseline was strongly associated with acquisition of syphilis. Lower level of seminal MCP-1 was associated with both presence of genital CMV shedding and syphilis acquisition. Future studies with anti-CMV therapeutics could help determine underlying mechanisms and if causal associations exist.

THURSDAY, FEBRUARY 26, 2015

Session P-C8 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Aging and Immune Senescence

305 Early Start of ART Affects Late Markers of Immune Senescence

Sharon L. Karmon; Teresa H. Evering; Melissa La Mar; Martin Markowitz

Aaron Diamond AIDS Research Center, an Affiliate of the Rockefeller University, New York, NY, US

Background: Despite a dramatic increase in life expectancy, people with HIV on antiretroviral therapy (ART) continue to suffer from higher risks of morbidity and mortality, often due to non-AIDS related illnesses. It is hypothesized that this increased risk is in part due to ongoing immune activation and premature immune senescence. We studied whether initiation of ART during primary HIV infection (PHI) correlated with improved markers of inflammation and immune senescence.

Methods: We recruited 32 subjects: 12 HIV+ men who started ART during PHI (Group 1), 10 HIV+ men who deferred ART until chronic HIV infection (CHI, Group 2) and 10 HIV-negative controls (Group 3). All subjects were men who have sex with men (MSM) between 18 - 45 years old with no comorbid chronic infections, immune modulating conditions/treatments, or IV drug use, and matched for EBV, CMV and RPR status. HIV-positive subjects were stably virologically suppressed. We used subject serum and plasma samples to perform ELISA, ECL, and xMAP assays to measure levels of soluble factors. We cryopreserved peripheral blood mononuclear cells (PBMCs) for flow cytometric measurements.

Results: Group 1 subjects began ART 31 ± 9 days after their estimated date of infection (EDOI) with HIV-1 and had been treated for 8.1 years at the time of screening. Group 2 began ART 3.7 ± 1.6 years after their EDOI and had been treated for 5.3 years. Group 1 subjects had higher CD4 counts (901 versus 605 cells/mm^3 and CD4/CD8 T cell ratios (1.81 versus 0.89) compared to Group 2. The median plasma levels of inflammatory markers (CRP, fibrinogen, IL-1b, IL-6, TNF-a) were statistically the same between all groups (see table). Other markers of immune dysregulation (% monocytes, sCD14, CD8 T cell activation, Th17/Treg ratio) were equally abnormal in both HIV+ groups compared to the HIV-negative controls. However, Group 1 subjects did exhibit improved values in several markers of immune senescence (naïve/memory T cell ratio, % terminally differentiated CD8 T cells, % senescent CD4+ T cells, marker of vaccine response in CD4 T cells, CD8 T cell telomere lengths) compared to Group 2 subjects.

		Group 1 (HIV+, started ART during PHI)		Group 2 (HIV+, started ART during CHI)		Group 3 (HIV-negative)			
		Median	IQR	Median	IQR	Median	IQR	p-value	Results
Markers of immune senescence	Naïve/Memory T cell ratio	1.86	0.96 - 2.6	0.71	0.57 - 1.6	0.47	0.30 - 1.8	0.0360	G1 > G2/G3
	Terminally differentiated CD8+T cells (%CD27-CD28-)	19.1	15.2 - 32.0	39.1	30.0 - 44.8	22.7	9.4 - 34.1	0.0386	G2 > G1/G3
	Senescent CD4+ T cells (%CD28-CD57+)	1.54	1.2 - 1.9	3.29	1.7 - 5.6	1.12	0.89 - 2.6	0.0057	G2 > G1/G3
	Marker of vaccine response (%CD4+CD28+)	53.8	53.1 - 68.4	37.3	29.4 - 47.4	50.7	40.2 - 56.8	0.0006	G1 > G2
	Telomere lengths in CD8+ cells (relative to 1301 cells)	13.8	13.0 - 14.4	11.8	8.0 - 13.1	13.7	12.0 - 15.2	0.0116	G2 < G1/G3
Markers of immune activation / coagulation	Plasma CRP (mg/L)	0.36	0.19 - 0.95	0.24	0.13 - 0.32	0.22	0.13 - 0.60	0.2008	NS
	Plasma Fibrinogen (mg/dL)	207	165 - 444	196	180 - 325	175	147 - 247	0.3550	NS
	Plasma IL-1β (ng/mL)	0.26	0.18 - 0.32	0.23	0.08 - 0.34	0.23	0.15 - 0.38	0.5139	NS
	Plasma IL-6 (ng/mL)	0.93	0.54 - 1.2	1.02	0.76 - 1.6	0.90	0.62 - 1.0	0.2395	NS
	Plasma TNF-α (ng/mL)	6.18	5.0 - 8.2	6.38	5.7 - 8.8	5.00	4.2 - 5.4	0.9006	NS
	Monocytes (% of CD3- lymphocytes)	2.50	2.1 - 4.8	2.23	1.4 - 7.3	1.17	0.55 - 1.7	0.0300	G1/G2 > G3
	Serum sCD14 (ng/mL)	2035	1848 - 2280	1930	1805 - 2055	1510	1395 - 1605	0.0003	G1/G2 > G3
	Activated CD8+ T cells (% CD38+HLA-DR+)	1.45	1.2 - 2.5	1.80	1.2 - 2.6	1.11	0.60 - 1.4	0.0433	G1/G2 > G3
	Th17/Treg ratio	0.36	0.24 - 0.43	0.33	0.28 - 0.44	0.46	0.41 - 0.71	0.0145	G1/G2 < G3

Results of study assays. PHI = primary HIV infection; CHI = chronic HIV infection; ART = antiretroviral therapy; IQR = interquartile range; G1/G2/G3 = Groups 1/2/3; NS = non significant

Conclusions: Initiation of ART during primary HIV-1 infection correlated with normalization of markers of immune senescence. Timing of ART initiation did not appear to correlate with any difference in select markers of inflammation or immune activation. These improvements in senescence markers may further support early treatment in patients with HIV.

306 Chronic HIV Infection Exacerbates Cellular Aging Markers in Isolated T-Cell Subsets

Anthony Hsieh; Beheroze Sattha; Hélène Côté
CIHR Team in Cellular Aging and HIV Comorbidities in Women and Children (CARMA cohort)
University of British Columbia, Vancouver, Canada

Background: Shorter telomere in the expanded senescent $CD8^+$ T cell compartment is an age-related immunologic abnormality reported in a small cohort study of people living with HIV. This immune defect, along with imbalance in $CD4^+$ and $CD8^+$ T cell distributions may link chronic HIV infection with premature age-related comorbidities, even in people treated with combination ART (cART). Little is known about markers such as telomere length (TL) and mitochondrial DNA apparent oxidative damage (mtDNA AOD) in isolated immune compartments during HIV infection. Our objective was to characterize these aging markers in $CD4^+$ and $CD8^+$ T cell subsets, and explore the possible role of HIV/cART on modulating immune aging. We hypothesized that HIV infection and factors such as viral load or time since diagnosis would be associated with skewed immune aging markers.

Methods: In this pilot study, live PBMCs were obtained from 33 HIV^+ subjects and 10 HIV^- controls enrolled in the CARMA cohort study. FACS was used to isolate $CD4^+$, proliferative $CD8^+$ $CD28^+$, and senescent $CD8^+$ $CD28^-$ T cells, as well as $CD19^+$ B cells. Relative TL and mtDNA AOD were measured in all cell subsets with sufficient cell count using qPCR. Results were compared using Spearman's correlation, two-tailed Mann-Whitney tests, and ANCOVA.

Results: As expected, a decreased $CD4^+/CD8^+$ T cell ratio (n=43, median 0.24 vs. 1.75, $p<0.001$) and an expanded senescent $CD8^+CD28^-$ T cell subset (n=43, 39 vs 17% of total T cells, p=0.02) were observed in the HIV^+ group compared to the HIV^- group. HIV infection was associated with shorter TL in proliferative $CD8^+CD28^+$ T cells (n=27, 3.35 vs. 3.73, p=0.02), but not in $CD8^+CD28^-$ or $CD4^+$ T cells after adjusting for age. Within the entire cohort, older age was associated with shorter TL in $CD4^+$ (n=26, R=-0.45, p=0.02), and proliferative $CD8^+CD28^+$ (n=27, R=-0.47, p=0.01) but not senescent $CD8^+CD28^-$ cells (R=-0.06). MtDNA AOD correlated with lifetime cART duration in both $CD8^+CD28^-$ and $CD8^+CD28^+$ T cells (n=22, R=0.53, p=0.01, and n=22, R=0.45, p=0.04). No relationship was seen between current HIV viral load, CD4 current or nadir, or time since diagnosis, and the aging markers assayed here.

Conclusions: Taken together, these results suggest a potential relationship between HIV infection and shorter TL in proliferative $CD8^+$ T cells. In contrast, cART duration was related to mtDNA oxidative damage in $CD8^+$ T cells, suggesting that cumulative exposure may play a role in mitochondrial aging in this immune compartment.

307 Age Associated Increases in Markers of Microbial Translocation and Inflammation in HIV-1 Infection

Eileen Scully[1]; Ainsley Lockhart[1]; Lisa Huang[2]; Marisol Romero-Tejeda[1]; Mary Albrecht[4]; Chrstine D. Palmer[1]; Ronald Bosch[3]; Marcus Altfeld[1]; Daniel Kuritzkes[2]; Nina Lin[5]
[1]Ragon Institute of MGH, MIT and Harvard, Jamaica Plain, MA, US; [2]Brigham and Women's Hospital, Boston, MA, Boston, MA, US; [3]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [4]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US; [5]Boston University School of Medicine, Boston, MA, US

Background: The aging of the HIV-1 infected population obligates a focus on the interaction of the virus with aging and comorbid conditions. Enhancing the survival and quality of life of infected individuals requires identification of the etiologic drivers of these pathologies in order to disrupt pathways leading to non-AIDS morbidity and mortality.

Methods: We recruited a cohort of HIV-1 infected men aged ≤35 years (n=22) or ≥50 years (n=23) on fully suppressive antiretroviral therapy (ART). Cryopreserved PBMCs were analyzed for T cell activation, exhaustion, proliferation, and innate cellular subsets. Functional capacity of the innate compartment was assessed by intracellular cytokine staining after stimulation with a panel of Toll-like receptor (TLR) agonists. Plasma markers of inflammation were measured, and selected analytes compared to an age-matched cohort of 46 uninfected men.

Results: No differences in T cell activation, exhaustion, proliferation or CD4/CD8 ratio were observed between age groups. Distributions of monocyte subsets (classical, nonclassical and intermediate), and myeloid and plasmacytoid dendritic cells were comparable. Innate functional capacity as measured by TNFa, IL-1b and IP-10 production by the relevant cell populations was not significantly different in response to TLR2, TLR3, TLR4, and TLR7/8 agonists. Analysis of plasma levels of cytokines identified elevated expression of the chemokine MCP-1 in the older age stratum ($p<0.05$, Mann-Whitney), which was confirmed by increased levels of mRNA expression ($p<0.05$). The ≥50 age group also showed higher levels of LPS as measured by the LAL assay ($p<0.05$). When compared to a group of uninfected control subjects, older HIV-1 infected adults were more frequently in the upper quartile of sCD14 expression (OR 4.12, 95% CI 1.06-16.0, $p<0.05$, chi square) compared to the age ≤35 HIV-infected and uninfected groups.

Conclusions: In a cohort of HIV-infected individuals well-matched on virologic parameters and separated into age strata, there was a significant difference in levels of plasma MCP-1 and markers of microbial translocation in the absence of significant differences in adaptive or innate cellular markers of immunosenescence, or in the functional assessment of innate immune capacity. Together, the data suggest that exploration of MCP-1 and LPS as a potential early signature of risk for age-related comorbidities is warranted.

THURSDAY, FEBRUARY 26, 2015

Session P-C9 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Immune Pathogenesis of IRIS

308 Vitamin D, D-Dimer, IFNγ and sCD14 Predict IRIS in a Prospective Multicenter Study

Laura W. Musselwhite[1]; Ann Tierney[2]; Susan Ellenberg[2]; Pablo F. Belaunzarán-Zamudio[5]; Adam Rupert[3]; Ian Sanne[4]; Michael M Lederman[6]; Juan Sierra-Madero[5]; Irini Sereti[7]

[1]Duke University, Durham, NC, US; [2]University of Pennsylvania, Philadelphia, PA, US; [3]Leidos Biomedical Inc., Reston, VA, US; [4]University of the Witwatersrand, Johannesburg, South Africa; [5]Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico; [6]Case Western Reserve University, Cleveland, OH, US; [7]National Institutes of Health (NIH), Bethesda, MD, US

Background: Immune reconstitution inflammatory syndrome (IRIS) in AIDS patients initiating anti-retroviral therapy (ART) is driven by immune dysregulation mechanisms. Biomarkers are needed to identify patients at risk.

Methods: Two hundred sixty-seven ART naïve patients with CD4 <100 cells/uL were enrolled in a multicenter, randomized placebo controlled ART initiation trial in South Africa and Mexico to test whether maraviroc added to an ART regimen could prevent IRIS. Participants were followed longitudinally for 6 months and IRIS events were reviewed prospectively based on the ACTG criteria. Pre-ART cryo-preserved plasma was used to measure cytokines (IFNγ, TNFα, IL-1β, IL-6, IL-10, IL-17), markers of myeloid cell activation (sCD14, sCD163), coagulation (D-dimer), CRP and vitamin D. Biomarkers with skewed distributions were log transformed prior to comparisons. Biomarkers in patients who developed IRIS were compared to the remaining cohort that did not develop IRIS after 6 months of follow-up. Biomarkers were then individually tested while adjusting for significant covariates selected through forward stepwise selection.

Results: Participants had a median age of 36, median CD4 count of 43 cells/μL, and median HIV-RNA 5.4 log10 copies/mL. Sixty-two participants developed IRIS and of these 21% were TB-IRIS. Patients who developed IRIS were more likely to be male (79% vs. 62%), with a prior AIDS–defining illnesses (79% vs. 54%), and a lower median hemoglobin (11.9 vs. 12.3 g/dL). Prior to ART, lower vitamin D, higher D-dimer, IFNγ, and sCD14 were independently associated with risk for IRIS in a multivariate analysis. A subgroup analysis of TB-IRIS cases (N=21) vs. patients without TB-IRIS was performed and revealed baseline levels of IFNγ, CRP, and sCD14 were independent predictors of TB-IRIS risk, while vitamin D levels were not associated with TB-IRIS in univariate or multivariate analyses.

Table 1. Biomarker levels in AIDS patients

Biomarker	IRIS	No IRIS	Unadjusted p-value	Adjusted p-value
IFNγ (pg/mL)	5.65 (2.25, 10.6)	2.72 (1.44, 5.17)	<0.001	0.01*
CRP (mg/L)	4.54 (1.84, 13.7)	2.47 (1.27, 8.99)	0.03	0.28
IP-10 (pg/mL)	3.43 (3.19, 3.59)	3.31 (3.10, 3.49)	0.005	0.16
TNFa (pg/mL)	19.9 (15.4, 28.1)	15.5 (12.1, 21.9)	0.042	0.23
sCD14 (μg/mL)	2400 (1988, 3235)	2014 (1645, 2471)	<0.001	0.01*
IL-6 (pg/mL)	2.48 (1.49, 4.02)	1.71 (1.23, 3.08)	0.048	0.48
IL-8 (pg/mL)	10.5 (6.61, 15.4)	7.62 (4.84, 13.8)	0.04	0.79
IL-10 (pg/mL)	14.0 (9.38, 20.3)	7.60, 15.7)	0.04	0.19
Vitamin D (ng/mL)	8.22 (4.99, 13.8)	9.65 (5.83, 17.9)	0.038	0.04*
D-Dimer (mg/L)	1.32 (0.84, 2.34)	0.85 (0.52, 1.52)	<0.001	0.008*

Data represent medians with interquartile ranges. * Denotes significance after multivariate adjustment for gender, hemoglobin, and prior AIDS-defining illness.

Conclusions: Biomarkers of T cell and monocyte activation (IFNγ, sCD14), coagulation (D-dimer) and low vitamin D prior to ART initiation are independently associated with IRIS. Further evaluation of these biomarkers as possible clinical prediction tools or targets of intervention for IRIS prevention is warranted.

309 LC-MS Analysis of Metabolites Differentiating IRIS From Non-IRIS in ACTG Study A5221

Mary A. De Groote[1]; Laura Ashton[1]; Marisa Harton[1]; Sam Bokatzien[2]; Kristofor Webb[1]; Carlos Adriano Matos de Silva[1]; Reem Al-Mubarak[1]; Sebabratra Mahapatra[1]; Diane Havlir[3]; John Belisle[1]

[1]Colorado State University, Fort Collins, CO, US; [2]National Jewish Health, Denver, CO, US; [3]University of California San Francisco, San Francisco, CA, US

Background: Immune reconstitution inflammatory syndrome (IRIS) occurs with potent treatment of HIV in the setting of co-infections such as *M. tuberculosis* (Mtb). IRIS is associated with substantial morbidity and mortality. We sought to better understand this syndrome and to develop a metabolic biosignature in plasma from subjects that developed IRIS. Samples were obtained from subjects enrolled in the immediate treatment arm of ACTG study A5221.

Methods: Subjects from the IRIS and Non-IRIS were matched for age, gender, and CD4 cells by the ACTG Data Center. Plasma samples from as many as 3 time points per subject (entry, IRIS window and follow-up) were analyzed. Plasma was extracted in triplicate with methanol and analyzed by liquid chromatography-mass spectrometry (LC-MS). LC-MS data were analyzed with Mass Profiler Professional (MPP) software (Agilent, Inc.) and XCMS online (Scripps Institute) to select molecular features (MFs) that distinguished IRIS and non-IRIS samples based on statistical significance.

Results: Each triplicate revealed 2,000-5,000 MFs and these were down selected based on a FC of 1.5 between IRIS and non-IRIS at each time point with a significance of $p<0.05$. The greatest difference between the IRIS and non-IRIS samples was observed with the IRIS window time point and included 59 MFs for all replicates analyzed. Four metabolomics databases (METLIN, HMDB, MTB LIPID MAPS and LIPID MAPS) were searched to provide a putative identification of the MFs. MF presumed to be small peptides and lipids (triglycerides, glycosphingolipids, vitamin D metabolites) dominated the signature. Some of the putative lipids are in well-known inflammatory pathways. Each significant MF was manually crossed checked against our in-laboratory Mtb lipid database and no matches were found, leading us to believe that the lipid molecules identified are of host origin. Targeted LC-MS analyses are currently underway to confirm identities and further assess changes in lipid metabolism of IRIS subjects.

Conclusions: These studies provide evidence that a biosignature based on metabolites can separate IRIS from non-IRIS early in the course of disease and may be able to predict those at risk for IRIS. Lipid species appear in our discriminatory signature. Efforts are ongoing to formally identify each of the significant MF we discovered. Ultimately we aim to confirm and validate our findings using samples collected in prospective trials or sites studying HIV/Mtb co-infected individuals who develop IRIS.

310 Associations Between Plasma Cytokine and Microbial Translocation Biomarkers and IRIS

Margaret A. Fischl[2]; Linda J. Harrison[1]; Varghese George[2]; Margaret Roach[2]; Xiao-Dong Li[3]; David Asmuth[3]; Pablo Tebas[4]; Camlin Tierney[1]; Catherine Godfrey[5]; Savita Pahwa[2]

[1]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, US; [2]University of Miami Miller School of Medicine, Miami, FL, US; [3]University of California Davis, Sacramento, CA, US; [4]University of Pennsylvania, Philadelphia, PA, US; [5]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

Background: IRIS is a pathogen-specific inflammatory response associated with ART initiation. We conducted a nested case-cohort study among subjects in a large prospective randomized longitudinal clinical trial (A5202) in the USA and investigated 18 plasma biomarkers of inflammation and microbial translocation for their association with risk of IRIS.

Methods: ACTG A5202 compared ABC/3TC or TDF/FTC combined with ATV/r or EFV for first-line HIV treatment. IRIS events were defined using ACTG criteria; unmasking and paradoxical events were included. 51 of 1452 subjects with baseline CD4<350 cells/mm^3 developed IRIS (3.9 cases/100 person years). We analyzed 100 randomly selected subjects (94 non-IRIS, 6 IRIS, stratified by pre-enrollment CD4≤200 cells/mm^3) and 45 additional IRIS cases. Plasma samples at baseline (n=141), an early time-point (~week 4, n=138) and week 48 (n=136) were tested for tumor necrosis factor (TNF), sTNF receptor I, sTNF receptor II, granulocyte colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP-1), interferon (IFN) gamma, IFN alpha 2, IFN gamma inducible protein 10 (IP-10), IL-1 beta, IL-2, IL-6, IL-8, IL-10, IL-12, IL-17, sCD14 (ELISA, Luminex or electrochemiluminescence), lipopolysaccharide (LPS, Limulus amebocyte lysate assay) and 16s ribosomal (r) DNA(PCR).

Cox models, stratified by pre-enrollment CD4 and weighted for the case-cohort design, evaluated associations between baseline biomarkers and time to first IRIS event. Logistic models evaluated associations between biomarker levels at week 4 and 48 and IRIS.

Results: The 145 subjects included 79% male (34% with AIDS history), median age 39 years, baseline HIV-1 RNA 4.8 (IQR 4.6-5.4) $\log_{10}$c/ml, CD4 84 (30-184) cells/mm^3.

At baseline, higher IP-10, LPS, sCD14, 16s rDNA and IFN alpha 2 were associated with greater risk of IRIS (Table). There was a significant (p=0.012) non-linear relationship between MCP-1 and IRIS. These results were supported by adjusted models; other biomarkers had p≥0.15.

Most biomarkers (TNF, sTNFRII, G-CSF, MCP-1, IP-10, IL-8, IL-10, IFN alpha 2, LPS, sCD14) decreased after ART initiation. IP-10 and LPS at week 4 were still associated with IRIS. At week 48, this association only remained for IP-10.

Table Title: Biomarkers with Significant (p-value <0.05) Associations with IRIS

Time-point	Biomarker	Inter-Tertile Range (33rd-67thcentile) or %>detection limit	Effect Type	Unadjusted RR, 95% CI	Unadjusted P-value	Adjusted RR, 95% CI	Adjusted P-value
Baseline	IP-10 (pg/ml) (n=137)	1370-3795	per inter-tertile range	1.6 (1.2, 2.2)	0.005	1.7 (1.1,2.5)	0.014
	LPS (pg/ml) (n=141)	162-228	per inter-tertile range	1.7 (1.3, 2.3)	<0.001	1.8 (1.2,2.6)	0.006
	sCD14 (ng/ml) (n=141)	1580-2082	per inter-tertile range	2.1 (1.5, 3.0)	<0.001	2.1 (1.2,3.7)	0.008
	16s rDNA (copies/ul) (n=141)	32-58	per inter-tertile range	1.4 (1.1, 1.9)	0.017	1.4 (1.1,2.0)	0.018
	IFN alpha 2 (pg/ml) (n=141)	46%	≤10.9 (detection limit) >10.9	1.0 (ref) 2.8 (1.4, 5.6)	0.003	1.0 (ref) 3.4 (1.3, 9.0)	0.011
	MCP-1 (pg/ml) (n=141)	218-342	lower tertile middle tertile upper tertile	1.0 (ref) 0.5 (0.2, 1.3) 2.1 (1.0, 4.5)	0.005	1.0 (ref) 0.4 (0.1, 1.1) 1.4 (0.5, 3.8)	0.042
Early (~Week 4)	IP-10 (pg/ml) (n=123)	699-1745	per inter-tertile range	1.6 (1.2, 2.2)	0.004	1.6 (1.1,2.2)	0.008
	LPS (pg/ml) (n=138)	174-244	per inter-tertile range	2.2 (1.5, 3.3)	<0.001	2.3 (1.5,3.6)	<0.001
Week 48	IP-10 (pg/ml) (n=131)	402-849	per inter-tertile range	1.4 (1.1, 1.8)	0.004	1.4 (1.1,1.9)	0.010
	LPS (pg/ml) (n=136)	148-204	per inter-tertile range	1.4 (1.0, 1.9)	0.095	1.2 (0.8,1.8)	0.34

Table Footer: IP-10, LPS and soluble CD14 were modeled on the $\log_{10}$ scale, RR = risk ratio (hazard ratio at baseline and risk ratio at early and week 48 time-points), CI = confidence interval, Unadjusted = adjusted for pre-enrollment CD4 ≤200 cells/mm^3 by design, Adjusted = additionally adjusted for baseline HIV-1 RNA, CD8 percent, history of AIDS, and randomized ACTG A5202 treatment

Conclusions: Enhanced systemic inflammatory response presumably through persistent monocyte activation and bacterial translocation in immunosuppressed patients appear important in the pathogenesis of IRIS and may be useful to predict risk for IRIS

311 Potential Role of IL-1 and IL-10 Pathways in IRIS Pathogenesis

Ainhoa Perez-Diez; **Elizabeth Richards**; Stig Jensen; Eleanor M. Wilson; Virginia Sheikh; Maura M. Manion; Bruno Andrade; Timothy Myers; Irini Sereti

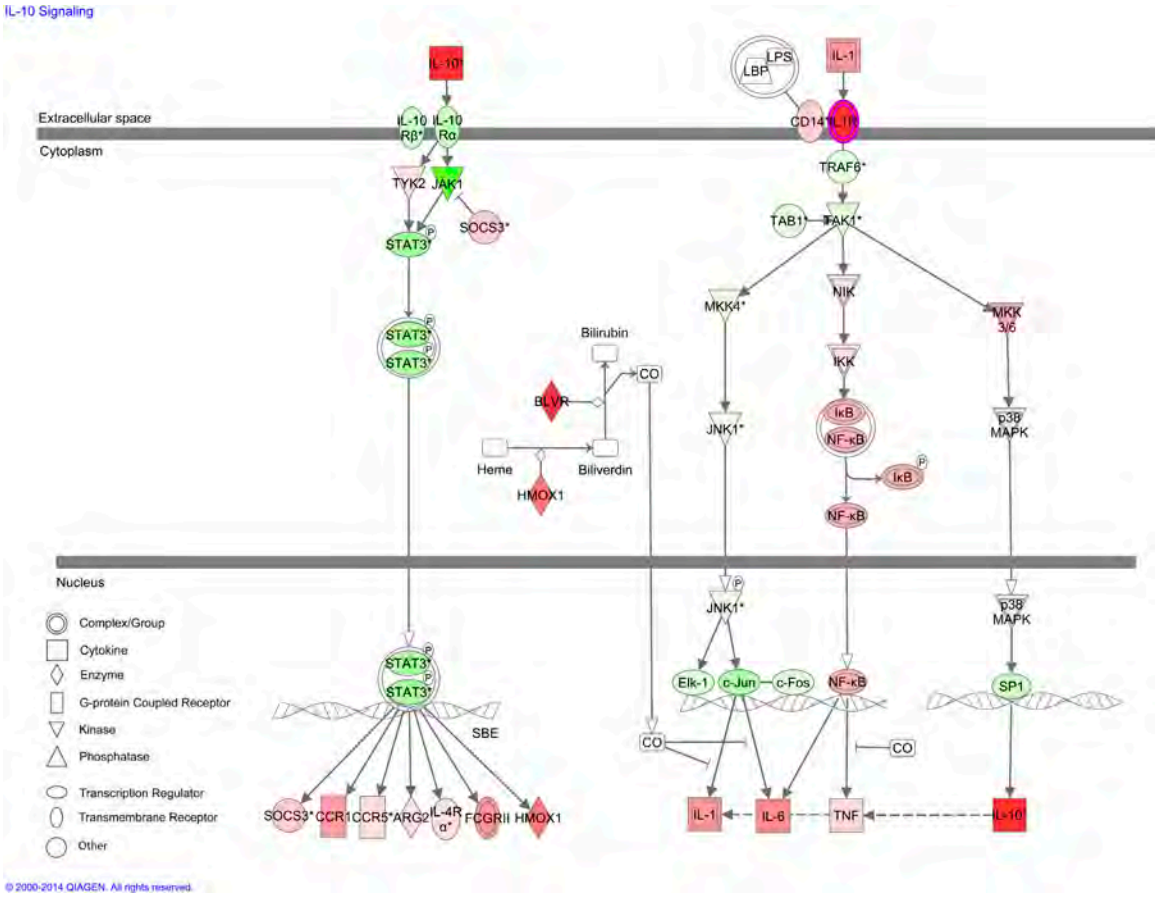
National Institute of Allergy and Infectious Diseases (NIAID), Rockville, MD, US

Background: Inflammation and immune activation play a central role in HIV pathogenesis. An exuberant inflammatory response, termed Immune Reconstitution Inflammatory Syndrome (IRIS), occurs in a subset of patients shortly after starting antiretroviral therapy (ART), and is more common in those with severe lymphopenia and underlying opportunistic infections. The pathogenesis and etiology of IRIS remain unclear. Microarray analysis of patient samples prior to ART initiation could allow the unbiased study of genes and molecular signatures in patients before they develop clinical manifestations of IRIS and help us understand the molecular pathways triggering the syndrome.

Methods: Gene expression profiles were measured by microarray analysis of peripheral mononuclear cells (PMC) obtained before ART from 143 HIV+ patients. Data were initially analyzed by the non-supervised method Principal Component Analysis (PCA), followed by supervised methods using Ingenuity Pathway Analysis (IPA). To detect which molecular

pathways (if any) might be over-represented in patients that would later develop IRIS we focused on biological function terms as well as upstream regulators that showed statistical significance of 10^{-7} in IPA.

Results: From a completed longitudinal cohort of ART-naive patients with CD4 <100 cells/μL starting ART, PMC were available from 143 patients pre-ART. Patients had a median age of 38 (IQR 30-45) years, CD4 22 (IQR 9-48) cells/μL and plasma HIV VL 4.99 (IQR 4.45-5.36)$\log_{10}$ copies/mL. Thirty six of them (25%) developed IRIS, based on ACTG criteria, at a median of 29 (IQR 7-56) days after ART initiation. PCA did not result in clear discrimination of PMC from IRIS versus non-IRIS patients, suggesting that at the time of analysis, before ART initiation, both groups looked similar at the molecular level. The most striking biological theme suggested by IPA analysis was expression of specific gene subsets associated with inflammatory responses and apoptosis/necrosis. Specifically, the IL-10 and IL-1 molecular pathways were highlighted in IRIS samples (Figure).



Differential gene expression for transcripts canonical pathway "IL-10 Signaling". Literature curated interactions between gene products are portrayed by shapes indicating type of gene product, while colors indicate the magnitude of difference in mRNA expression observed in this study. Transcripts in red were more abundant in IRIS patients, in green were more abundant in non-IRIS.

Conclusions: This study highlights possible molecular pathways, such as IL-1 and IL-10, involved in IRIS etiology that might have important implications for IRIS prevention and treatment. In addition, these findings may have implications for the diagnosis and treatment of complications in patients recovering from lymphopenia caused by etiologies besides HIV.

WEDNESDAY, FEBRUARY 25, 2015

Session P-C10 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Immune Activation and HIV Pathogenesis

312 Inflammatory Biomarkers Decline but Do Not Normalize After 10 Years of cART

Kenneth A. Lichtenstein[1]; Carl Armon[2]; Vijaya Knight[1]; Rafeul Alam[1]

[1]National Jewish Health, Denver, CO, US; [2]Children's Hospital Colorado, Aurora, CO, US

Background: HIV infection is characterized by a state of chronic inflammation (CI). The degree to which combination antiretroviral therapy (cART) contributes to or ameliorates CI over time is unclear.

Methods: We measured levels of several inflammatory biomarkers (IB) in the 10 year period following initiation of cART in 327 patients participating in the Study to Understand the Natural History of HIV Infection in the Era of HAART (SUN Study) who had HIV-RNA levels < 200 copies/ml at each measurement. IB levels were measured in the specimen proximal to initiation of cART in 40 cART-naïve (cART-N) SUN Study patients and in a single specimen obtained from each of 30 case-matched HIV-negative controls (HNC). Baseline characteristics were similar between cART-experienced (cART-E) and cART-N groups. Frozen serum specimens were analyzed for RANTES, TNF-alpha, MIP-1 alpha and beta, MCP-1,

and Interleukin (IL)-6, IL-7, and IL-15. In the cART-E group, IBs were measured at study entry, 2 years and 6 years. We stratified the 3 IB samples by number of years receiving continuous cART. We used the Kruskal-Wallis test of medians to compare IB levels from the cART-E vs. the cART-N and HNC groups.

Results: Over the 10 years following initiation of ART, IB levels in the cART-E group were significantly higher vs. those of HNCs ($p < 0.05$) excepting IL-7 which was not significantly different (NS) vs. HNCs. In the first 4-5 years IB levels in the cART-E groups initially rose and then declined to levels below those of the cART-N group but the differences were NS with the exception of MIP-1 alpha that was lower for the last 3 years and IL-6, IL-15, and MCP-1 that were lower in year 10 ($p < 0.05$, for all). For each year, there were no significant differences in IBs in the PI vs. NNRTI groups.

Median biomarker values among 327 SUN Study patients who had viral loads < 200 copies/mL when biomarker levels were done by years of ARV experience compared to median values among 40 ARV naives and 30 HIV-negative matched controls

Year	N	RANTES	p. naives	p. controls	TNF-α	p. naives	p. controls	MIP-1α	p. naives	p. controls	MIP-1β	p. naives	p. controls	IL-6	p. naives	p. controls	IL-7	p. naives	p. controls	IL-15	p. naives	p. controls	MCP-1	p. naives	p. controls
1	56	13375	↑	↑	9.96	·	↑	824	·	↑	247	↑	↑	0.00	·	↑	4.35	↓	↑	6.02	·	↑	371	·	↑
2	76	14037	↑	↑	19.89	·	↑	938	·	↑	256	↑	↑	1.81	·	↑	5.82	↓	↑	5.51	·	↑	361	·	↑
3	78	14330	↑	↑	18.78	·	↑	891	·	↑	254	↑	↑	3.24	·	↑	5.89	↓	↑	6.00	↑	↑	333	·	↑
4	70	13913	↑	↑	14.41	·	↑	833	·	↑	241	↑	↑	0.00	·	↑	2.05	↓	·	2.73	·	↑	305	·	↑
5	62	14635	↑	↑	0.00	·	↑	904	·	↑	267	↑	↑	0.00	·	↑	2.69	↓	·	5.69	·	↑	345	·	↑
6	80	12467	↑	↑	0.00	·	↑	704	·	↑	239	↑	↑	0.00	·	↑	0.00	↓	↓	0.00	·	↑	275	·	↑
7	100	12975	↑	↑	8.04	·	↑	796	·	↑	239	↑	↑	0.00	·	↑	0.00	↓	·	1.08	·	↑	316	·	↑
8	76	12236	↑	↑	8.94	·	↑	660	↓	↑	222	·	↑	0.00	·	↑	0.00	↓	·	0.00	·	↑	235	·	↑
9	62	13457	↑	↑	0.00	·	↑	692	↓	↑	228	·	↑	0.00	·	↑	0.00	↓	·	0.00	·	↑	299	·	↑
10	128	13450	↑	↑	7.00	·	↑	645	↓	↑	234	·	↑	0.00	↓	↑	0.00	↓	·	0.00	↓	↑	259	↓	↑
Naives	N=40	10087			11.43			795			198			5.49			14.99			4.31			370		
Controls	N=30	9868			0.00			256			147			0.00			1.45			0.00			146		

Legend: ↑=p-value indicates significantly higher (p<0.05) median value compared to naives or controls; ↓=p-value indicates significantly lower (p<0.05) median value compared to naives or controls; · = non-significant difference compared to naives or controls. Statistical test used: Kruskal-Wallis test of medians.

Conclusions: After 10 years of cART, levels of IBs decline but remain elevated vs. HNCs. There were no significant differences in levels seen with PI vs. NNRTI based cART.

313 Persistently High IL-18 and sCD14 Are Independently Associated With Clinical Failure

Ashwin Balagopal[1]; Nikhil Gupte[1]; James Hakim[2]; Mina C. Hosseinipour[3]; Nagalingeswaran Kumarasamy[4]; Andrea Cox[1]; Ian Sanne[7]; David Asmuth[5]; Thomas Campbell[6]; Amita Gupta[1]
On behalf of the ACTG

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe; [3]University of North Carolina, Chapel Hill, NC, US; [4]Y.R.G. Care, Chennai, India; [5]University of California San Diego, San Diego, CA, US; [6]University of Colorado, Denver, CO, US; [7]ACTG, Washington, DC, US

Background: Inflammation drives clinical progression in HIV-infected persons. Antiretrovirals (ARV) partially reduce inflammation. We studied the effect of persistent inflammation on clinical failure during ARV among multi-country ACTG 5175 trial participants.

Methods: In a nested case-control study, cases were clinical failure, defined as incident WHO stage 3/4 HIV disease or death from weeks 24 to 96 weeks; controls were without clinical failure and randomly selected. IL-6, IP-10, IL-18, TNFα, IFNγ and sCD14 levels were measured pre-ARV and at week 24 of ARV (ARV24). Persistent inflammation was defined as highest quartile levels (>Q3) pre-ARV and at ARV24 for IL-6(>48.3pg/mL),IP-10(>2856pg/mL),IL-18 (>774pg/mL), sCD14 (>6.4$\log_{10}$pg/mL), TNFα(>28.4pg/mL), and IFNγ(>48pg/mL), compared to lower quartiles(≤Q3). Poisson regression analysis was used to estimate RRs, adjusting for baseline age, sex, treatment, country, CD4, $\log_{10}$HIV RNA, prevalent TB, and viral suppression at ARV24 (HIV RNA<400 cp/ml).

Results: Of 99 cases and 233 controls, available samples were tested (**Figure**). Median age was 34 years; 160 (48%) were females. Median (IQR) CD4 was 181 (96-229) cells/μL and median (IQR) HIV RNA level was 5 (4.5-5.5) $\log_{10}$ cp/mL. At ARV24, 276 (87%) persons were virologically suppressed; median (IQR) CD4+ T cell count was 290 (197-388) cells/μL. Persistently high levels of IL-18 and sCD14 at ARV24 were independently associated with clinical failure [IL-18 RR (95%CI) 3.59 (1.48–8.74), p<0.05; sCD14 RR (95%CI) 2.21 (1.01–4.80), p<0.05]. High levels of IFNγ were independently associated with decreased risk of clinical failure [RR (95%CI) 0.08 (0.01–0.66), p<0.05]. Other markers at ARV24 were not associated with clinical failure. Restricting the analysis to subjects who were virologically suppressed at ARV24 maintained associations with IL-18 and IFNγ [IL-18 RR (95%CI) 3.10 (1.08–9.02), p<0.05; IFNγ RR (95%CI) 0.07 (0.01 – 0.64), p<0.05]; the association with sCD14 diminished in significance [RR (95%CI) 2.0 (0.77 – 5.25), p=0.16].

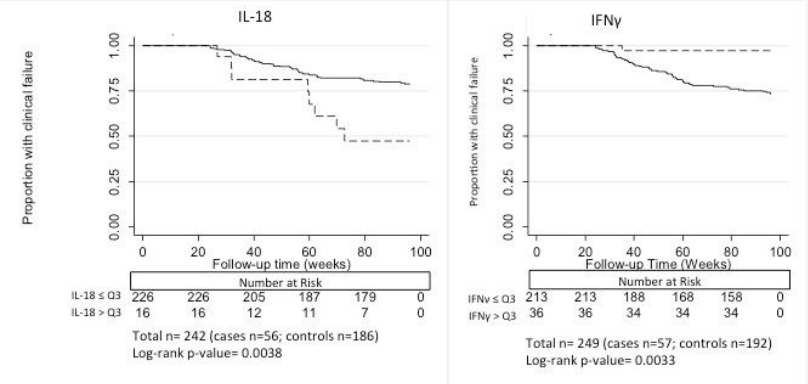


Figure. Kaplan-Meier survival estimates of HIV-infected persons initiating ARV in multi-national settings and their rate of developing clinical failures in persons with high (>Q3) compared to low (≤Q3) inflammatory marker levels.

Conclusions: IL-18, a highly pro-inflammatory cytokine linked to organ damage, was associated with clinical failure in persons who were virologically suppressed in diverse settings, suggesting that persistent inflammation in HIV-infected persons on ARV may contribute to further disease progression. Unexpectedly, IFNγ levels were inversely related to the risk of clinical failure, suggesting a link with immune restoration.

314 Impact of Partner HIV Status on Immune Activation and Inflammation During Chronic HIV

Shameem Z. Jaumdally[1]; Pamela Gumbi[1]; Hoyam Gamieldien[1]; Anabela Picton[2]; Caroline Tiemessen[2]; Lindi Masson[1]; Lenine Liebenberg[3]; David Coetzee[1]; Anna-Lise Williamson[1]; Jo-Ann Passmore[1]

[1]University of Cape Town, Cape Town, South Africa; [2]National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg, South Africa; [3]Centre for AIDS Programme Research in South Africa, Durban, South Africa; [4]University of Cape Town, Cape Town, South Africa

Background: The role of immune activation and inflammation on the rate of HIV disease progression has been proposed as a critical determinant of pathogenesis, but the mechanism is not fully understood. HIV+ individuals with HIV- partners (discordant relationship) versus HIV+ partners (concordant relationship) provide valuable insight to the role of continued HIV exposure on the clinical course of HIV infection. This study compared the impact of systemic viral load, T cell activation and inflammatory cytokine profiles on rate of disease progression in HIV+ concordant and discordant couples.

Methods: The impact of sexual partner status on systemic immune activation and inflammatory cytokine production in HIV+ individuals in HIV concordant (n=195) or discordant (n=142) long-term relationships was determined by flow cytometric analysis and luminex assays. Sequencing and qPCR were performed to determine CCR5 haplotypes.

Results: HIV+ concordant individuals had 0.5 Log_{10} higher plasma viral loads than HIV+ discordant ones ($p<0.0001$), and this was maintained over 24 months. However, this did not predict worse disease outcome (measured by absolute blood CD4 counts at later time points). HIV+ concordant individuals had higher frequencies of activated T-cells (CD3+CD38+CCR5+) in blood than HIV+ discordant counterparts. Individuals with plasma HIV loads >1500 copies/ml had higher frequencies of CD4+CCR5+ ($p=0.007$), CD8+CD38+ ($p=0.01$) and CD8+HLA-DR+CD38+ ($p=0.01$) T-cells compared to individuals with plasma viral loads <1500 cps/ml. CCR5 promoter haplotypes were not found to be a determinant in the CCR5 expression levels by T-cells. HIV+ concordant individuals had significantly higher concentrations of IL-1β ($p=0.04$) and TNF-α ($p=0.03$) in plasma than HIV+ discordant individuals. In women, plasma viral loads predicted genital tract viral loads ($Rho=0.65$; $p<0.0001$), with HIV+ concordant women having higher genital viral loads than HIV+ discordant women ($p=0.001$). HIV+ women with detectable HIV in genital secretions had higher genital concentrations of IP-10 ($p=0.002$), IL-1α ($p=0.007$), IL-1β ($p=0.004$), IL-6 ($p=0.005$), IL-8 ($p=0.008$), MCP-1 ($p=0.03$), MIP-1β ($p=0.01$), IL-10 ($p=0.01$), and G-CSF ($p=0.002$) than those with no detectable genital HIV.

Conclusions: This study suggests that partner's HIV status influences systemic viral loads, immune activation and inflammation, and is potentially a key factor ensuring continued HIV replication, but did not influence disease outcome.

315 Pretherapy Inflammation and Long-Term CD4 Response to Antiretroviral Therapy

Amit C. Achhra[1]; Andrew N. Phillips[2]; Sean Emery[1]; Rodger D. MacArthur[3]; Hansjakob Furrer[4]; Stéphane De Wit[5]; Marcelo H. Losso[6]; Matthew G. Law[1]
On behalf of the INSIGHT SMART and FIRST Study groups

[1]Kirby Institute, University of New South Wales, Sydney, Australia; [2]University College London, London, United Kingdom; [3]Wayne State University, Detroit, MI, US; [4]University Hospital Bern, Bern, Switzerland; [5]Saint-Pierre University Hospital, Brussels, Belgium; [6]Hospital J.M. Ramos Mejía, Buenos Aires, Argentina

Background: Pre-antiretroviral therapy (ART) inflammation/ coagulation activation predict clinical outcomes. However, it is unknown whether these processes result in blunted CD4+ count (CD4) responses to ART, thereby resulting in clinical outcomes. The objective of this analysis was to perform exploratory analyses assessing whether pre-ART inflammatory marker levels predicted the CD4 response to ART.

Methods: Analyses were based on data from the SMART and FIRST trials. The SMART study was an international trial evaluating continuous (viral suppression (VS) versus interrupted (drug conversation (DC)) ART and the FIRST trial evaluated 3 first-line ART regimens with ≥2 classes. For this analysis, participants had to be ART-naïve or off ART at randomisation and (re)starting ART and have C-reactive protein (CRP), interleukin-6 (IL-6) and D-dimer measured (available at randomisation for the majority of SMART participants and a selected group from FIRST who participated in previous biomarker studies). Using random effects linear models, we assessed the association between each of the biomarker levels, categorised as quartiles, and change in CD4 from ART-start to 24 months post-ART. Analyses adjusted for pre-ART CD4, study arm, follow-up time and other known confounders. Sensitivity analyses included separate analyses by trials (given it was a selected sub-sample in FIRST) and excluding the DC arm in SMART.

Results: Overall, 1084 individuals (659 from SMART (26% ART naïve) and 425 from FIRST) met the eligibility criteria, providing 8264 CD4 measurements. 75% were male with the mean age of 42 years, 37% and 47% were white and black respectively, and 10% and 33%, respectively, were hepatitis B and C positive. The median (inter-quartile range) baseline CD4 (cells/mm^3) were 360 (265-473) overall and 416 (350-530) and 100 (22-300) in SMART and FIRST, respectively. All of the biomarkers were inversely associated with baseline CD4 in FIRST but not in SMART. The figure shows the mean change in CD4 post-ART by quartiles of CRP, IL-6 and D-dimer. In adjusted models, there did not appear to be any clear relationship between changing biomarker levels and mean change in CD4 (P for trend: CRP: 0.97; IL-6: 0.25 and D-dimer: 0.29). Sensitivity analyses yielded similar results.

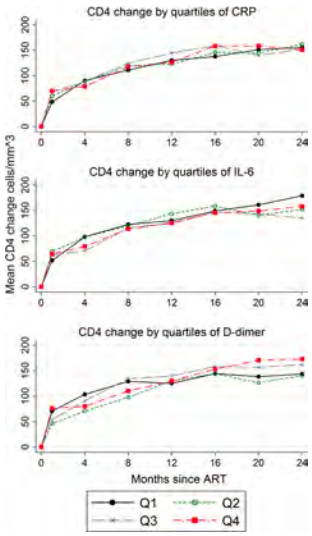


Figure: Change in CD4 count since (re)initiation of ART by pre-ART quartiles of CRP, IL-6 and D-dimer. Q=quartile (e.g. Q1= 1st quartile etc.).

Conclusions: Pre-ART inflammation/coagulation activation do not predict CD4 response to ART and appear to influence the risk of clinical outcomes through mechanisms other than by blunting long-term CD4 gain.

316 Plasma Levels of sCD163 Predict All-Cause Mortality From HIV Infection

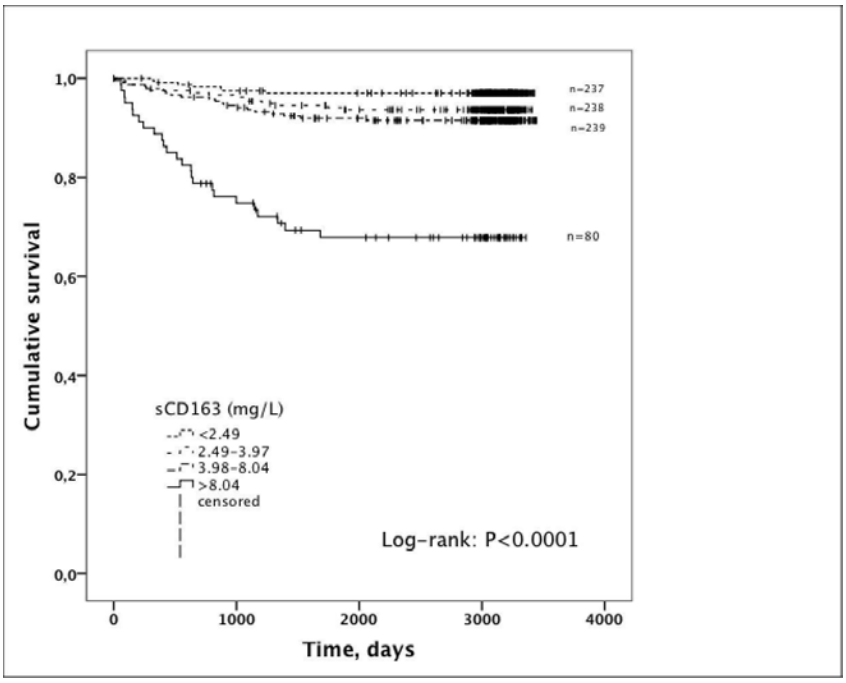
Troels Bygum Knudsen[1]; Janne Petersen[2]; Holger Jon Møller[3]; Søren Moestrup[4]; Jesper Eugen-Olsen[2]; Gitte Kronborg[1]; Thomas Benfield[1]

[1]Copenhagen University Hospitals, Hvidovre, Copenhagen, Denmark; [2]Copenhagen University Hospitals, Hvidovre, Copenhagen, Denmark; [3]Aarhus University Hospital, Aarhus, Denmark; [4]Aarhus University, Aarhus, Denmark

Background: CD163, a monocyte- and macrophage-specific scavenger receptor, is shed from the cell surface as soluble CD163 (sCD163) during activation. Monocyte/macrophage activation may contribute to on-going low-grade inflammation in human immunodeficiency virus (HIV)-infected patients. We therefore investigated the role of monocyte activation by measuring sCD163 levels in relation to outcome from HIV infection.

Methods: Plasma sCD163 levels were measured in 794 individuals with HIV infection in 2004/5. The prognostic value of sCD163 was evaluated by Cox proportional hazards regression analysis after adjustment for other risk factors. Kaplan-Meier survival curves were constructed for 0-30, 31-60, 61-90 and 91-100 percentiles. All values are median and interquartile range.

Results: Individuals were 42 (IQR: 37-50) years old and 72% were male. 43% were men who had sex with men (MSM), 36% were heterosexuals (HSX) and 15% injection drug users (IDU). 86% were receiving antiretroviral treatment (ART). Baseline CD4 T cell count was 502 (348-705) per μl and HIV RNA <20 (<20-87) copies/mL. Plasma sCD163 was 3.39 (2.27-5.07) mg/L. During 8.4 (8.1-8.8) years of follow up, there were 67 deaths (8.4%). Individuals who died had significantly higher sCD163 levels than survivors. In adjusted analysis, the mortality increase per mg of sCD163 was 8% (Hazard rate (HR): 1.08, 95% confidence interval (CI): 1.05-1.12). Age (HR: 1.07 (95% CI: 1.05-1.10) per year increment) and IDU vs. no IDU (HR: 2.30 (95% CI: 1.27-4.15) were other independent predictors of death while higher CD4 T cell counts (HR: 0.18 (95% CI: 0.09-0.37) per log increment) were associated with a decreased risk of death. In time-updated analysis, ART did not affect outcome (HR: 1.32 (0.59-2.95). The top 10% group of sCD163 had a 5-fold increased risk of death compared to the lowest 30% group (HR: 5.75 (95% CI: 2.20-15.02) (Figure 1).



Conclusions: The study verifies a clear association between the scavenger receptor system of macrophages and survival in HIV-infected individuals suggested by previous studies. It is the first to demonstrate a highly significant increase in mortality among HIV-infected individuals with an excessive activation of their monocyte/macrophage system. Our findings show that sCD163 is a novel prognostic marker and suggest that monitoring monocyte/macrophage activation may be important in HIV infection.

317 Immunologic Pathways That Predict Mortality in HIV+ Ugandans Initiating ART

Sulggi A. Lee[1]; Helen Byakwaga[2]; Yap Boum[2]; Tricia Burdo[3]; Yong Huang[1]; Jessica Haberer[5]; Annet Kembabazi[2]; David R. Bangsberg[5]; Jeffrey Martin[1]; Peter W. Hunt[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Mbarara University of Science and Technology, Mbarara, Uganda; [3]Boston College, Boston, MA, US; [4]University of California San Francisco, San Francisco, CA, US; [5]Massachusetts General Hospital and Harvard University, Boston, MA, US

Background: Abnormal immune activation persists in most HIV-infected individuals despite prolonged antiretroviral therapy (ART)-mediated viral suppression, and predicts increased morbidity and mortality, but the specific immunologic pathways predicting disease remain incompletely defined, particularly in resource-limited settings. Plasma kynurenine/tryptophan (KT) ratio, a marker of indoleamine 2,3-dioxygenase-1 (IDO) activity, strongly predicts mortality in this setting, but whether it is simply a marker for other immunologic pathways is unclear.

Methods: We sampled the first 542 HIV-infected Ugandans initiating ART in the UARTO cohort and measured plasma KT ratio, D-dimer, IL-6, sCD163, sCD14, and T cell activation (%HLA-DR+CD38+) at baseline and month 6 of ART-mediated viral suppression (<400 copies/ml). Predictors of mortality were assessed with Cox proportional hazards models, adjusted for age, body mass index, and pre-ART CD4+T cell count.

Results: Participants were mostly female (70%) with a median age of 34, and had advanced disease (median baseline CD4+ count 140 cells/mm^3 and HIV RNA 5.0 $\log_{10}$copies/mL) at ART initiation. A total of 43 deaths occurred during a median 7 years of follow-up, with just 10% LTFU at 7 years. As previously reported, both pre-ART and month 6 KT ratio predicted increased mortality. In addition, pre-ART D-dimer, IL-6, and sCD14 were associated with increased mortality in unadjusted and adjusted models. After 6 months of ART-mediated suppression, IL-6 and sCD14 remained significant predictors of mortality, but CD4+ and CD8+ T cell activation were associated with even greater risks of death. However,

further adjustment for KT ratio rendered mortality associations with all other biomarkers non-significant. The association between KT ratio and mortality persisted despite adjustment for all other biomarkers, with the possible exception of IL-6 at month 6 (HR 1.75, 95% CI 1.00, 3.01).

Biomarker	Pre-ART aHR (95% CI)[a]	Pre-ART + KT Ratio Adjustment	Month 6 ART aHR (95% CI)[a]	Month 6 ART +KT Ratio Adjustment
KT ratio (log_{10}nM/uM)	**1.98 (1.34, 2.91)**	--	**2.26 (1.38, 3.68)**	--
Pre-ART CD4+ count (cells/mm^3)	**0.39 (0.22, 0.69)**	**0.40 (0.22, 0.72)**	0.34 (0.11, 1.04)	0.45 (0.16, 1.32)
D-dimer (log_{10}ug/mL)	**2.36 (1.56, 3.56)**	**2.21 (1.44, 3.39)**	1.69 (0.91, 3.13)	1.52 (0.75, 3.07)
IL-6 (log_{10}pg/mL)	**1.73 (1.36, 2.18)**	**1.66 (1.28, 2.15)**	**1.98 (1.28, 3.06)**	1.63 (0.99, 2.67)
sCD163 (log_{10}ug/L)	0.95 (0.62, 1.46)	0.79 (0.52, 1.20)	1.32 (0.67, 2.59)	0.89 (0.42, 1.92)
sCD14 (log_{10}ug/L)	**2.33 (1.41, 3.84)**	**1.79 (1.00, 3.20)**	**1.97 (1.09, 3.57)**	1.46 (0.75, 2.84)
CD4+ T cell activation	1.14 (0.63, 2.03)	0.92 (0.52, 1.64)	**2.54 (1.21, 5.35)**	1.62 (0.77, 3.41)
CD8+ T cell activation	1.26 (0.76, 2.09)	1.09 (0.65, 1.81)	**2.64 (1.26, 5.56)**	1.97 (0.94, 4.15)

[a] Per interquartile range increase, adjusted for age, BMI, and pre-ART CD4+ T cell count. [b] Per interquartile range increase, adjusted for age, BMI, pre-ART CD4+ T cell count, and log_{10}KTratio. *Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; aHR, adjusted hazard ratio per interquartile range increase; IL-6, interleukin-6; KT ratio, ratio of kynurenine to tryptophan; sCD163, soluble CD163; sCD14, soluble CD14.*

Conclusions: The immunologic pathways predicting mortality among HIV-infected Ugandans may be different than those described in resource-rich settings. IDO and T cell activation may have a greater impact during early ART in resource-limited settings where opportunistic infections remain an important cause of death. These findings also suggest that monocyte (sCD14) and T cell activation may predict mortality via the same causal pathways as IDO, while IL-6 may predict mortality via overlapping but potentially distinct pathways.

318 Immune Activation Impairs Yellow Fever Vaccine Efficacy in HIV-Infected Patients

Vivian I. Avelino-Silva[1]; Karina T. Miyaji[1]; Marisol Simoes[2]; Marcos Freire[2]; Ana Sartori[1]; Peter W. Hunt[3]; Karine Milani[1]; Augusto Mathias[1]; Ana Paula Batista[1]; Esper G. Kallas[1]

[1]University of Sao Paulo Medical School, Sao Paulo, Brazil; [2]Fundaçao Oswaldo Cruz, Rio de Janeiro, Brazil; [3]University of California San Francisco, San Francisco, CA, US; [4]University of Sao Paulo Medical School, Sao Paulo, Brazil

Background: While highly immunogenic in healthy vaccinees, Yellow Fever vaccine (YFV) induces weaker and less durable immune responses in HIV-infected individuals. Chronic immune activation may impair cellular and humoral responses to YFV in HIV-uninfected individuals, but little is known about the immunologic predictors of YFV response in HIV infection. We enrolled HIV-infected and –uninfected adults who received YFV to evaluate predictors of immunity, as assessed by specific neutralizing antibody (NAb) titers.

Methods: 18-65 year-old volunteers who received a single YFV dose despite time since vaccination were eligible. All HIV-infected participants were ART-suppressed. Participants with diabetes, chronic liver, renal, or rheumatologic diseases, or prior cancer (except Kaposi Sarcoma) or immunosuppressive therapy were excluded.

Results: Among 34 HIV-infected and 58 HIV-uninfected participants, median age was 46 and 38 years old, respectively, and more HIV-infected volunteers were men (79% vs. 29%). Median time since YFV was somewhat shorter in HIV-infected (42 months) than in HIV-uninfected participants (69 months). Few participants in either group recalled adverse events after YFV. Compared to HIV-uninfected controls, HIV-infected participants had lower median $CD4^+$ T cell counts (790 vs.1120/mm^3, p<0.0001) and $CD4^+/CD8^+$ ratios (0.69 vs. 1.83, p<0.0001). Mean log_{10}NAb titers were also significantly lower in HIV-infected than HIV-uninfected participants (3.3 vs. 3.6, p=0.044), a difference that remained significant after adjustment for age, gender, and time since vaccination (p=0.024). In HIV-infected participants, lower NAb titers were associated with longer time since YFV (rho: -0.38, p=0.027) and lower $CD4^+/CD8^+$ ratio (rho: 0.42, P=0.014), but not $CD4^+$ T cell count (p=0.519). None of these factors were associated with NAb titers in HIV-uninfected participant.

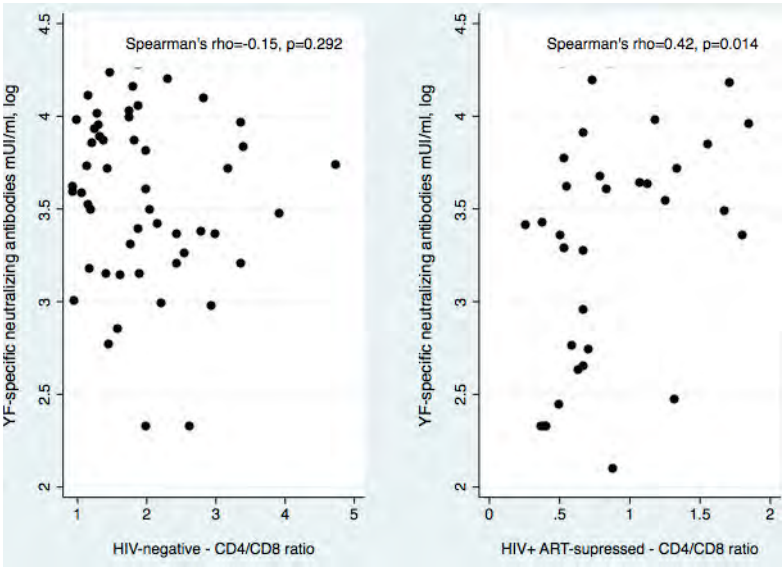


Figure 1: Relationship between CD4/CD8 Ratio and YF Neutralizing Ab Titer in HIV-infected and –uninfected Participants.

Conclusions: Treated HIV-infected individuals appear to have impaired and/or less durable neutralizing antibody responses to YFV than HIV-uninfected individuals, which were associated with lower $CD4^+/CD8^+$ ratio. These results suggest that a low $CD4^+/CD8^+$ ratio may be a better surrogate for functional immune defects than the $CD4^+$ T cell count in treated HIV infection. Our findings are consistent with an emerging literature suggesting that $CD4^+/CD8^+$ ratio is a stronger correlate of chronic immune activation and predictor of mortality in this setting.

319 Association Between sCD163 and CMV IgG in Virologically Suppressed HIV+ Patients

Aimee Hodowanec[1]; Brett Williams[1]; Barbara Hanson[1]; Britt Livak[2]; Sheila Keating[3]; Nell Lurain[1]; Oluwatoyin M. Adeyemi[4]

[1]Rush University Medical Center, Chicago, IL, US; [2]University of Chicago, Chicago, IL, US; [3]Blood Systems Research Institute/University of California San Francisco, San Francisco, CA, US; [4]Ruth M Rothstein CORE Center, Chicago, IL, US

Background: HIV+ patients with controlled viremia have ongoing chronic inflammation which has been associated with an increased risk for cardiovascular and neurocognitive disease. Cytomegalovirus (CMV) has been implicated as a potential driver of this inflammation. Soluble CD163 (sCD163) is a marker of monocyte/macrophage activation and is upregulated in inflammatory states. We explore the relationship between CMV and sCD163 in HIV+ pts with well controlled viremia.

Methods: Patient samples and data from existing cohorts of HIV+ subjects with undetectable HIV RNA were utilized for this study. Specimens were collected between 2009 and 2013. ELISA was used to measure sCD163 level in plasma and CMV immunoglobulin G (IgG) level in serum. All subjects underwent plasma CMV PCR testing. Bivariate analysis (Pearson Correlation and Kruskal Wallis Test) and multivariate linear regression analysis were performed to identify variables associated with CMV IgG level. Variables included in the multivariate model are sex, race, age, duration of antiretroviral use, and sCD163 level.

Results: Of 139 adult, virologically suppressed HIV+ subjects, 130 (94%) were CMV seropositive and were included in our analysis. The median age was 55 (51-59) years, 63% male, 61% black, 18% Hispanic, 12% white, and 2% other race. The median CD4 count was 512 (193-696) cells/mm^3, median sCD163 was 1171.3 ng/mL (886.7-1554.1), and median CMV IgG level was 39.0 IU/mL (32.0-46.0) (results reported as median (IQR) unless stated otherwise). No subjects had detectable plasma CMV DNA. Bivariate analysis revealed a significant, positive correlation between sCD163 and CMV IgG levels ($r = 0.19$, $p = 0.03$) and a trend towards increased CMV IgG among those with coronary disease ($H = 2.99$, $p = 0.08$). Multivariate analysis also identified a positive relationship between CMV IgG levels and sCD163 (coef. 0.004; 95%CI 0.001-0.003 $p = 0.01$).

Conclusions: Among HIV+ adults with undetectable HIV RNA, increased CMV IgG level (even in the absence of CMV viremia) is associated with increased sCD163 level. Our finding adds to the body of evidence suggesting that CMV is involved in the complex pathophysiology of chronic inflammation in HIV. Cellular correlates of these elevated CMV IgG levels deserve further exploration.

WEDNESDAY, FEBRUARY 25, 2015

Session P-C11 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Manipulating Immune Activation

320 The mTORC1 Inhibitors, Temsirolimus and Everolimus, Suppress HIV Patient-Derived CD4+ T-Cell Death and Activation In Vitro

Clovis S. Palmer[1]; Matias Ostrowski[4]; Jingling Zhou[1]; Linda Lam[1]; Alan Landay[2]; Anthony Jaworowski[1]; Joseph M. McCune[3]; Suzanne M. Crowe[1]

[1]Burnet Institute, Melbourne, Australia; [2]Rush University Medical Center, Chicago, IL, US; [3]University of California San Francisco, San Francisco, CA, US; [4]Instituto de Investigaciones Biomédicas en Retrovirus y SIDA, Buenos Aires, Argentina

Background: Activated T cells support their energetic and biosynthetic demands in part by increasing glucose uptake and glycolysis. Glucose transporter 1 (Glut1), the major glucose transporter on T cells, is essential for CD4+ T cell activation and effector functions, and its expression is increased on CD4+ T cells in HIV-infected subjects. High Glut1 expression on CD4+ T cells is associated with immune activation/inflammation and low CD4 cell count, irrespective of treatment status. We hypothesized that experimental inhibition of glycolysis in activated CD4+ T cells would inhibit HIV-induced cell death and supress the production of inflammatory mediators.

Methods: Flow cytometry was used to examine Glut1 expression on CD4+ T cells from 58 virologically supressed HIV+ males (viral load <50 RNA copies/ml), 40 immunological responders (median CD4: 700), 18 immunological non-responders (median CD4: 246), and 29 HIV- male controls. Glut1-expressing CD4+ T cells ($CD4_{Glut1}$) were sorted on a FACSAria machine. Glycolytic inhibition was achieved using the mTORC1 inhibitors, temsirolimus or everolimus. Cell death was measured by a trypan blue exclusion. Secreted L-lactate levels served as a measure of glycolytic activity and cytokine levels were determined by ELISA.

Results: The proportion of $CD4_{Glut1}$ cells was significantly elevated in immunological non-responders (median: 14.8, IQR: 11.7-36.9, $p<0.0001$) compared to responders (median: 8.4, IQR: 5.4-12.3) and HIV- controls (median: 4.9, IQR: 1.6-6.9, $p<0.0001$). $CD4_{Glut1}$ cells purified from HIV+/ART subjects underwent more rapid cell death in culture compared to CD4+ T cells not expressing Glut1. The in vitro death of both CD4+ T cell populations was markedly reduced when co-cultured with non-toxic concentrations of the temsirolimus or everolimus. Remarkably, both drugs at a concentration as low as 1 nM effectively suppressed glycolysis by 25-50% in CD4+ T cells that were activated *in vitro* with PMA and IL-2, with effects persisting beyond 7 days after exposure. Further, temsirolimus suppressed CD4+ T cell activation (as measured by HLA-DR expression) and TNF secretion by approximately 20 and 75%, respectively.

Conclusions: High glycolytic metabolism may be associated with accelerated CD4+ T cell death in HIV+ persons. These data suggest that periodic addition of the clinically safe mTORC1 inhibitors, temsirolimus or everolimus, to current ART regimen may reduce residual T cell activation and inflammation, and improve T cell recovery.

321 Decreased Monocyte Activation With Daily Acyclovir Use in HIV-1/HSV-2 Coinfected Women

Andrew D. Redd[1]; Kevin Newell[2]; Eshan U. Patel[1]; Fred Nalugoda[3]; Paschal Ssebbowa[3]; Sarah Kaliballa[3]; Ronald H. Gray[4]; Thomas C. Quinn[1]; David Serwadda[5]; **Steven J. Reynolds**[1]

[1]National Institute of Allergy and Infectious Diseases (NIAID), Washington, DC, US; [2]Clinical Research Directorate/Clinical Monitoring Research Program, Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, MD, US; [3]Rakai Health Sciences Program, Kalisizo, Uganda; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]Makerere University College of Health Sciences, Kampala, Uganda

Background: In two separate randomized control trials, acyclovir treatment of HSV-2/HIV coinfected individuals significantly reduced HIV viral load, and decreased the rate of disease progression. It is unclear if the protective effect of acyclovir use on HIV disease is a direct effect of decreasing HIV replication, or a secondary effect of decreased immune activation associated with less herpetic reactivation.

Methods: HIV-1/HSV-2 co-infected women from the Rakai Health Sciences Program, Uganda were enrolled in a double-blind randomized placebo-controlled trial to examine the effect of daily acyclovir use on HIV disease progression. Serum samples were collected at enrollment and every six months for two years (n=301).

High sensitivity CRP and sCD14 levels were measured on all available serum samples. Longitudinal analyses of treatment outcome were right-censored at initiation of HAART for those women who started therapy. The predictive value of CRP and sCD14 on survival was estimated using Kaplan-Meier survival curves and Cox proportional hazard regression models. Mixed-effects models were used to examine time varying CRP and sCD14 levels by study arm.

Results: Higher baseline levels of sCD14 were not associated with progression to HAART eligibility when adjusted for treatment arm, baseline CD4, and viral load. Higher CRP levels were also not predictive of disease progression. Levels of CRP increased in both arms, and were not significantly different (p=0.25). Levels of sCD14 decreased slightly in both arms, but at a significantly increased rate in the treated women (-0.003 $\log_{10}$ sCD14/month, 95% CI=-0.005- -0.002) compared to the placebo group (-0.001 $\log_{10}$ sCD14/month, 95% CI=-0.002-0.001; p=0.02), which was independent of HIV viral load and CD4 count (p=0.039). However, the decrease in sCD14 in the treatment group was small with a total change in levels of 0.072 $\log_{10}$ (290 ng/mL) over the two-year period, which is 15% of the mean sCD14 levels at baseline in the treatment group.

Conclusions: sCD14 levels decreased faster in the acyclovir treated arm than in the placebo arm independent of CD4 count and viral load. These data support the hypothesis that decreased monocyte activation may contribute in part to the slower HIV disease progression observed during daily acyclovir treatment.

322 Atorvastatin Reduced T-Cell Activation and Exhaustion Among Suboptimal Immune Responders: A Randomized Crossover Placebo Controlled Trial

Damalie Nakanjako

Makerere University Infectious Diseases Institute, Kampala, Uganda

Background: T-cell activation independently predicts mortality, poor immune recovery and non-AIDS illnesses during combination antiretroviral therapy (cART). Atorvastatin showed anti-immune activation effects among HIV-infected cART-naïve individuals. We hypothesized that adjunct atorvastatin therapy would reduce T-cell activation among cART-treated adults with suboptimal immune recovery.

Methods: A randomized double-blind placebo controlled cross-over trial, of atorvastatin 80 mg daily versus placebo for 12 weeks, among individuals with CD4 increase <295cells/μl after seven years of suppressive cART. Change in CD4 T-cell-activation (CD3+CD4+/CD8+ CD38+HLADR+) and CD8 T-cell-activation and in T-cell-exhaustion (CD3+CD4+/CD8+PD1+) were measured using flow cytometry.

Results: Thirty patients were randomized, 15 to each arm. Atorvastatin resulted in a 28% greater reduction in CD4 T-cell-activation (60% reduction) than placebo (32% reduction); p=0.001. Atorvastatin also resulted in a 35% greater reduction in CD8-T-cell-activation than placebo (49% versus 14%, p=0.0009), CD4 T-cell exhaustion (27% versus 17% in placebo), p=0.001, and CD8 T-exhaustion (27% versus 16%), p=0.004. There was no carry-over/period effect. Expected adverse events were comparable in both groups and no serious adverse events were reported.

Conclusions: Atorvastatin reduced T-cell immune activation and exhaustion among cART-treated adults in a Ugandan cohort. Atorvastatin adjuvant therapy should be explored as a strategy to improve immune recovery during antiretroviral therapy.

323 P2X Type Purinergic Antagonists Can Block HIV-1 Infection and Associated Inflammation

Talia Swartz; Meagan O'Brien; Anthony Esposito; Nina Bhardwaj; Benjamin Chen

Icahn School of Medicine at Mount Sinai, New York, NY, US

Background: HIV-1 causes a chronic, incurable infection that is associated with chronic inflammation. Even in the face of virologic suppression with antiretroviral therapy this inflammation can persist. The mechanism of this inflammation is not clearly understood. Purinergic receptors are known to be mediators of inflammatory responses and can contribute to pro-inflammatory cytokine production and lymphocyte cell death. Purinergic receptor signaling has been found to be important for HIV-1 infection and we have recently found that inhibition of the P2X subtype purinergic receptors potently blocks HIV-1 productive infection at the level of membrane fusion. This study examines whether virus-induced purinergic signaling is responsible for inflammatory cytokine release during HIV-1 infection.

Methods: Our laboratory has developed methods using fluorescent constructs of HIV-1 to evaluate productive infection by flow cytometry and confocal microscopy. Infected supernatants can be subjected to multiplex bead capture assays to test for an array of human cytokines including IL-12, IL-10, IL-8, IL-6, TNF, and IL-1β. We have tested the effect of HIV-1 infection on peripheral blood mononuclear cells and observed levels of pro-inflammatory cytokine production.

Results: We observe that HIV-1 productive infection in CD4 T lymphocytes is potently blocked by P2X selective inhibitors. We further observed that exposure of peripheral blood mononuclear cells to HIV-1 results in induction of pro-inflammatory cytokines including IL-1β and IL-6 and that these levels are reduced with P2X inhibition. This suggests that P2X inhibitors can block both HIV-1 productive infection and associated inflammation.

Conclusions: Our findings distinguish P2X receptors as key signaling mediators of HIV-1 infection and inflammation. Studies in progress will examine the mechanism of P2X signaling in HIV-1 entry and will test whether purinergic antagonists can block HIV and reduce inflammatory sequelae of HIV-infection in humanized mouse models. We are exploring whether these drugs could be used as adjunctive antiretroviral therapy that could serve to reduce the morbidity and mortality associated with HIV-1 chronic inflammation.

THURSDAY, FEBRUARY 26, 2015

Session P-C12 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Pathogenesis in Lymph Nodes

324 CD4$^+$ T cell death mediated by pyroptosis in early SIV infected lymphatic tissues

Wuxun Lu[1]; Guobin Kang[1]; Fangrui Ma[1]; Yanmin Wan[2]; Yue Li[1]; Mark Lewis[3]; Qingsheng Li[1]

[1]*University of Nebraska-Lincoln, Lincoln, NE, US;* [2]*Shanghai Public Health Clinical Center and Institutes of Biomedical Sciences, Fudan University, Shanghai, China;* [3]*BIOQUAL, Inc., Rockville, MD, US*

Background: Lymphatic tissues are the principle sites for HIV-1 replication, host-virus interaction and CD4$^+$ T cell loss. However, the current understanding of the virus-host molecular interaction in lymphatic tissues, especially in early infection, is limited. We thus investigated virus-host interaction in the lymph nodes (LNs) of rhesus macaques during early simian immunodeficiency virus (SIV) infection.

Methods: Sixteen adult male macaques were intra-rectally inoculated with SIVmac251 (3.1 x 10^4 $TCID_{50}$) and were euthanized at 3, 6, 10, 14 or 28 days post-inoculation (dpi); another 3 macaques were used as uninfected controls. Total RNA was isolated from rectal draining LNs of macaques and whole genome transcriptome was profiled using Illumina GAIIx, and genes with altered expression were identified and analyzed. SIV RNA in rectal draining LNs was quantified by using qRT-PCR and in situ hybridization (ISH). CD4$^+$ and caspase-1$^+$ cells in LNs were quantified using flowcytometry.

Results: SIV RNA was detected in all the animals euthanized at 6 and 10 dpi using both qRT-PCR and ISH, however, SIV RNA was only detected in 2 and 1 out of 3 animals at 3 dpi using qRT-PCR and ISH respectively. Transcriptome analysis showed that hosts had clear responses, with 103, 366 and 1350 differentially expressed genes (DEGs) at 3 dpi, 6 dpi and 10 dpi, respectively. Pathway analysis of DEGs at 6 dpi and 10 dpi pointed to the activation of pyroptosis in addition to innate immune response and inflammation pathways. Multiple genes in pyroptosis pathway were significantly up-regulated in expression. The active form of capase-1, the hallmark of pyroptosis activation, was quantified in $CD4^+$ T cells in rectal draining LNs using flowcytometry. Concurrent with loss of $CD4^+$ T cells in draining LNs after early infection, the level of caspase-1^+ $CD4^+$ T cells significantly increased, indicating that the pyroptosis mediated $CD4^+$ T cell death occurs in vivo in early SIV infected lymphatic tissues.

Conclusions: This study shows robust host responses to early SIV infection, the activation of pyroptosis pathway, and $CD4^+$ T cell loss mediated by pyroptosis in lymphatic tissues in *vivo*. Since $CD4^+$ T cell loss and immune activation are the hallmarks of HIV pathogenesis, the $CD4^+$ T cell loss mediated by pyroptosis and associated immune activation *in vivo* in early SIV infection identified in this study opens a new avenue to design interceptive strategy to prevent $CD4^+$ T cell death.

325 Fibrosis in Lymphoid Tissue Is Associated With Peripheral Blood Regulatory T Cells

Julie C. Gaardbo[1]; Patricia S. Nielsen[2]; Lise Mette R. Gjerdrum[3]; Karoline Springborg[4]; Elisabeth Ralfkiær[4]; Henrik Ullum[4]; Åse Andersen[4]; **Susanne D. Poulsen**[4]
Dr. Susanne D Poulsen, sdn@dadlnet.dk
[1]University of Copenhagen, Rigshospitalet, Copenhagen, Denmark; [2]Aarhus University Hospital, Denmark, Aarhus, Denmark; [3]Bispebjerg Hospital, University Hospital of Copenhagen, Denmark, Copenhagen, Denmark; [4]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

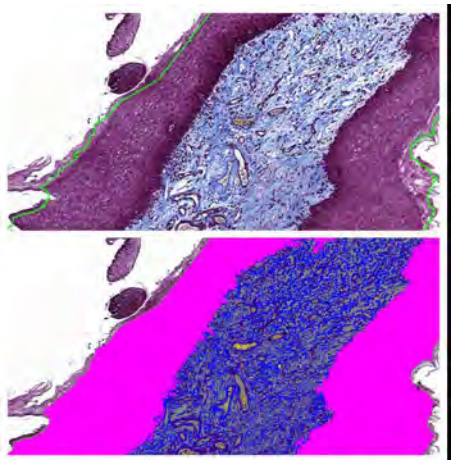
Background: HIV may damage the structure in lymphoid tissue replacing the functional space with collagen. Regulatory T cells (Tregs) have anti-inflammatory properties exerting their function in part by secretion of transforming growth factor beta (TGF-b) which is known to induce fibrosis. In pathogenic SIV infection tissue fibrosis induced by TGF-b1-postive Tregs has been demonstrated. Thus, Tregs may participate in the pathogenesis leading to fibrosis in lymphoid tissue in HIV infection as well. We hypothesized that lymphoid tissue fibrosis was associated with percentage of peripheral blood Tregs and the level of immune activation.

Methods: Tonsil biopsies from 27 HIV-infected patients were examined. All patients had been on cART for a minimum of two years, had CD4 nadir <250 cells/μL, and HIV RNA had been ≤20 copies/mL for at least two years prior to inclusion in the study.

Automated image analysis of tricrome-stained, paraffin-embedded tonsil biopsies determined the amount of fibrosis where $A_{fibrosis}$ was the area of fibrous connective tissue and A_{lesion} the area of the lesion including all tissue elements except epithelia, large lymphocyte clusters, and erythrocytes (see figure).

Based on fibrosis index patients were divided into two groups with low fibrosis (n=13) and high fibrosis (n=14). Tregs (CD4+CD25+$CD127^{low}$FoxP3+) and activated cells (CD4+CD38+HLA-DR+) were determined in peripheral blood using flow cytometry. Differences between groups were analysed using Mann-Whitney U-test. Results are given as median (IQR).

Results: The groups of patients with low fibrosis vs. high fibrosis were similar in regard to age, sex, current CD4 and CD8 cell counts, and CD4 nadir. The group with low fibrosis displayed lower percentage of Tregs compared to the group with high fibrosis (4.8% (4.4-6.9) vs. 6.9% (5.6-8.4), P=0.0186). This was accompanied by lower percentage activated CD4+ cells in low fibrosis vs. high fibrosis (1.5% (1.0-2.2) vs. 2.5% (1.8-4.2), P=0.0319).



Masson tricrome-stained tonsil biopsy and result of automated image analysis. Blue:Fibrous connective tissue; Pink: epithelia; yellow: erythrocytes; purple/grey: other tissue components.

Conclusions: Patients with low amount of fibrosis in tonsil tissue also exhibited low percentage Tregs and immune activation, suggesting Tregs to be involved in the pathogenesis of fibrosis in HIV-infected patients on cART

326 Decreased T_{FR}/T_{FH} Ratio in SIV-Infected Rhesus Macaques

Ankita Chowdhury; Perla Del Río-Estrada; Steven Bosinger; Guido Silvestri
Emory University, Atlanta, GA, US

Background: T follicular helper cells (T_{FH}) are critical for the development and maintenance of germinal centers (GC) and the humoral immune response. During chronic stages of HIV/SIV infection T_{FH} cells accumulate, possibly as a result of antigenic persistence. The SIV/HIV-associated T_{FH} expansion may also reflect a lack of regulation by suppressive follicular regulatory $CD4^+$ T cells (T_{FR}) . T_{FR} cells are natural regulatory T cells (T_{REG}) that migrate into the follicle and, similarly to T_{FH} cells, up-regulate CXCR5, Bcl6 and PD1.

Methods: Lymph node (LN) biopsies were obtained from SIV-infected and uninfected rhesus macaque (RM), as well as HIV-infected humans. T_{FR} cells were identified by flow cytometry and immunohistochemistry. Cell-associated viral DNA was measured by RT-PCR and next-generation RNA sequencing was performed on sorted populations from uninfected and SIV-infected RM by Illumina.

Results: We identified T_{FR} cells as $CD4^+$, $Foxp3^+$, $CXCR5^+$, $PD1^+$ and $Bcl6^+$ within LN of both humans and RM and confirmed their localization within the GC by immunohistochemistry. RNA sequencing showed that T_{FR} cells share a T_{FH} and T_{REG} transcriptional profile with intermediate expression of FoxP3, Bcl6, PRDM1, IL-10 and IL-21. In

healthy, SIV-uninfected RM, we observe a negative correlation between frequencies of T_{FR} cells and both T_{FH} (p=0.0358) and GC B cells (p=0.0140) as well as with levels of $CD4^+$ T cell proliferation (p=0.0315). Following SIV infection, the ratio of T_{FR} to T_{FH} cells was reduced (p=0.0058) with no change in the frequency of T_{REG} cells or in the frequency of T_{FR} cells within the total CD4 T cell pool. Finally, we examined whether higher levels of direct virus infection of T_{FR} cells might be involved in their relative depletion post-SIV infection. We found that T_{FH}, T_{FR} and T_{REG} cells sorted from SIV- infected RM harbor comparable levels of cell-associated viral DNA.

Conclusions: Our data suggests that T_{FR} cells may contribute to the regulation and proliferation of T_{FH} and GC B cells *in vivo* and that a decreased ratio of T_{FR}/T_{FH} cells in chronic SIV infection of RM may lead to unchecked expansion of both T_{FH} and GC B cells.

THURSDAY, FEBRUARY 26, 2015

Session P-C13 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Dissecting Pathogenesis Through In Vitro Studies

327 A Dual-Tropic HIV-1 Env Interacts With CCR5 to Deplete Bystander CD4 T Cells In Vitro and In Vivo

Li-Chung Tsao[1]; Haitao Guo[2]; Jerry Jeffrey[3]; James A. Hoxie[4]; Lishan Su[2]

[1]*University of North Carolina, Carrboro, NC, US;* [2]*University of North Carolina, Chapel Hill, NC, US;* [3]*GSK, Chapel Hill, NC, US;* [4]*University of Pennsylvania, Philadelphia, PA, US*

Background: Bystander CD4 T cell depletion during HIV-1 infection plays an important role in AIDS disease progression, a process is largely mediated by the HIV-1 Env protein. CCR5 is one of the two co-receptors required for HIV-1 binding and subsequent entry, but its involvement in Env-induced pathogenesis is poorly understood. In this report, we study the CD4 T cell pathogenesis caused by a dual-tropic HIV-1 virus R3A Env, focusing on the role of Env-CCR5 binding.

Methods: Using a cultured PBMC infection model or humanized mice in vivo, R3A can readily induce both infected CD4 T cell death and uninfected "bystander" CD4 T cell death. To study the involvement of Env-CCR5 binding, we utilized an Env-mutant of R3A, termed R3A-5,6AA, which has lost the potential for CCR5 binding.

Results: We found loss of CCR5-binding by the mutant R3A-5,6AA resulted in reduced pathogenesis of bystander CD4 T cells. Importantly, R3A-5,6AA can replicate to the same level as wild type R3A by using CXCR4-binding for virus entry. Accordingly, treatment of CCR5 antagonist TAK-779 inhibited bystander CD4 T cell death in R3A infection without affecting viral replication. In addition, stimulation of CCR5 using MIP1-β in R3A-5,6AA infection increases bystander CD4 T cell death. We have further confirmed our finding in vivo using a humanized mice model, and we observed bystander CD4 T cell pathogenesis in the spleen and bone marrow is dependent on CCR5 usage by the HIV-1 Env.

Conclusions: We provide the first evidence in physiologically relevant in vivo models that shows CCR5 binding by HIV-1 Env plays an important role in Env-induced depletion of bystander CD4 T cells.

328 Investigation of the Association of Gag-Protease Dependent Replication Capacities With Clinical Outcomes of HIV-1 Infection

Keiko Sakai[1]; Takayuki Chikata[1]; Hiroyuki Gatanaga[2]; Shinichi Oka[2]; Masafumi Takiguchi[1]

[1]*Kumamoto University, Kumamoto-shi, Japan;* [2]*National Center for Global Health and Medicine, Tokyo, Japan*

Background: Immune pressure by cytotoxic T lymphocytes (CTLs) induces escape mutations and immune evasion in HIV-1 infection, and the persistence of escape variants shapes HLA-associated viral diversity at the population level. Previous studies with Caucasian and African cohorts showed that HLA-associated Gag polymorphisms impose fitness cost and that Gag-Protease mediated viral replication capacity (Gag-Pro RC) is compromised in patients with protective HLA alleles. However, the protective alleles reported in Caucasian/Africa cohorts, including B*57:01, are not prevalent in Japan. Therefore, factors associated with protection are likely to be different in Asian populations due to different HLA distributions. Moreover, the role of Gag in HIV-1 disease progression has not been well defined in the Asian populations. To address these issues, we investigated HLA-associated changes in Gag-Pro RCs in a Japanese cohort.

Methods: We generated chimeric $HIV\text{-}1NL_{4\text{-}3}$ carrying *gag-protease* derived from 330 treatment-naive Japanese individuals who are chronically infected with HIV-1 subtype B. Replication capacities of chimeric viruses were determined by infecting CEM-GXR cells *in vitro*, which are engineered to express LTR-GFP, CCR5, and CXCR4. Subsequently, we examined the association of Gag-Pro RCs with clinical markers of HIV infection and the impact of patients' HLA alleles on Gag-Pro RCs.

Results: In contrast to Caucasian- and African-cohort studies, patients with higher Gag-Pro RCs showed only a weak tendency toward higher viral load (VL) and lower CD4 count. We did not observe statistically significant associations. Even though previous studies with Caucasian and African cohorts reported a stronger association of Gag-Pro RCs with patients' VL in the presence of protective HLA alleles such as HLA-B*57, our data indicated that subjects who did not carry Japanese-specific protective alleles, HLA-B*52 and -B*67, showed a statistically significant association between Gag-Pro RCs and VL. Furthermore, we found six locations in the Gag-Protease region, four of which was negatively correlated and the other two positively correlated with VL.

Conclusions: Taken together, our data suggested the impact of Gag-Pro dependent replication on HIV-1 disease progression in the absence of a protective immune pressure. The results also implied a different mechanism of HLA-induced changes in Gag-Pro RCs and their impact on clinical outcomes in the Japanese population compared to Caucasian and African cohorts.

329 Association of Bacteria-Induced IL-23 and Th17 Frequencies in HIV-1^+ Individuals

Jennifer Manuzak[1]; Sonia Amraoui[1]; Nipa Decroix[2]; Pierre Loulergue[2]; Odile Launay[2]; Marco Iannetta[1]; Jean-Baptiste Guillerme[1]; Lene Vimeux[1]; Anne Hosmalin[1]

[1]*Inserm U1016, Institut Cochin, Paris, France;* [2]*Centre d'Investigation Clinique CIC 1417, Inserm-AP-HP, Hôpital Cochin, Paris, France*

Background: Cytokine imbalances in HIV-1 infection could be mediated in part by the innate immune response to translocated intestinal microbes. Previous work showed that PBMC from HIV-1-infected patients ($HIV\text{-}1^+$) produce significantly more IL-23 in response to bacterial stimulation as compared to uninfected controls ($HIV\text{-}1^-$). Overproduction of IL-23 could skew T cell responses towards a Th17 phenotype. However, the relationship between microbial translocation, cytokine production and Th17 cell frequencies in the context of *in vivo* HIV-1 infection is not well understood. We compared IL-23 production and the frequency of Th17 cells in response to bacterial stimulation during HIV infection.

Methods: PBMC from 18 chronically infected $HIV\text{-}1^+$ and 21 $HIV\text{-}1^-$ donors were utilized. The frequency of Th17 cells ($IL\text{-}17A^+IFN\text{-}\gamma^-$) within memory $CD4^+$ T cells ($CD3^+CD4^+CD45RA^-$) of total PBMC was assessed either *ex vivo* on fresh PBMC or *in vitro* after stimulation with *E. coli* or *P. aeruginosa* using frozen PBMC by multi-parameter flow cytometry. Levels of IL-23 in PBMC culture supernatants after bacterial stimulation were assessed by ELISA. Statistical significance between the $HIV\text{-}1^+$ and $HIV\text{-}1^-$ groups was assessed using Mann-Whitney tests. Correlations were calculated using Pearson tests.

Results: The frequency of Th17 cells *ex vivo* was significantly increased in HIV-1$^+$ (n=15) as compared to HIV-1$^-$ (n=15; p=0.0001). In preliminary experiments, the median level of IL-23 production in HIV-1$^+$ (n=6) did not reach statistical significance over HIV-1$^-$ (n=6) after *in vitro* stimulation with *E. coli* (p=0.39) or *P. aeruginosa* (p=0.24). However, the correlation between the level of IL-23 production and the frequency of Th17 cells in HIV-1$^+$ was significant after stimulation with *E. coli* (n=6; p=0.01) and *P. aeruginosa* (n=6; p=0.02) stimulation.

Conclusions: We found increased frequencies of peripheral blood Th17 cells in chronic HIV-1$^+$ patients. This may be due to elevated cytokine production in response to translocated bacteria, as suggested by the relationship between IL-23 levels and Th17 frequencies after bacterial stimulation in HIV-1$^+$. Th17 cells are preferentially depleted in the intestinal mucosa of HIV-1$^+$, likely due to infection and killing of these cells. Our data suggest a potential mechanism by which the innate immune response to HIV-1-induced microbial translocation could promote the expansion, activation, viral infection and destruction of Th17 cells in the gut, thus contributing to HIV-1 disease pathogenesis.

330 Effect of Methamphetamine Use on T-Cell Proliferation In Vivo and Ex Vivo

Marta Massanella[4]; Sara Gianella[4]; Jennifer M. Dan[1]; Eric Daar[2]; Michael P. Dube[3]; Richard H. Haubrich[4]; Douglas D. Richman[4]; Davey M. Smith[4]; Sheldon Morris[4]; Rachel D. Schrier[4]

[1]La Jolla Institute of Allergy and Immunology, La Jolla, CA, US; [2]Los Angeles Biomedical Research Institute at Harbor–University of California Los Angeles Medical Center, Torrance, CA, US; [3]University of Southern California Keck School of Medicine, Los Angeles, CA, US; [4]University of California San Diego, La Jolla, CA, US

Background: Methamphetamine (METH) is a widely used recreational drug among HIV-infected men who have sex with men (MSM). Its use is associated with worse health outcomes in HIV-infected individuals. Here we investigated the effect of METH-use on immune function and virus shedding in semen.

Methods: Paired PBMC and semen samples were collected from our *in vivo* cohort of chronically HIV-infected MSM on suppressive ART (n=50, of whom 16 self-reported METH-use). PBMC were analyzed for markers of immune activation (CD38, HLA-DR and CD45RA), proliferation (Ki67) and exhaustion (PD-1) by flow cytometry. Seminal levels of cytomegalovirus (CMV) and HIV were quantified by real-time PCR. *Ex vivo* studies were performed on 19 HIV-infected individuals from a treated, but not uniformly suppressed cohort who tested positive for METH by urine toxicology (UTox+) and 19 HIV-infected UTox negative controls (matched for viral load and CD4 T-cell counts). PBMC proliferative responses to mitogen PHA and to CMV, candida, Mycobacterium tuberculosis, toxoplasma and HIV antigens were assayed in triplicate after 7 days of culture. T-cell proliferation was measured by [^{3}H]-thymidine incorporation; stimulation index was calculated as a ratio of the mean counts per minute (cpm) for each stimulus divided by the mean cpm of unstimulated controls. Mann-Whitney and Fisher exact tests were used for continuous and dichotomous data comparisons, respectively.

Results: METH-users had significantly higher CD4 and CD8 T-cell proliferation levels (Ki67$^+$, p<0.005 for both), CD4 T-cell activation (CD45RA$^-$CD38$^+$, p=0.005) and CD4-T cell exhaustion (PD-1$^+$, p=0.0004) compared to non-METH-users. In addition, the proportion of CMV or HIV shedding in METH-users was higher than in non-METH users (75% vs 26% [p=0.002] and 19% vs 3% [p=0.09], respectively). *Ex vivo* responses of the acute METH UTox+ patients confirmed higher spontaneous PBMC proliferation compared to controls (p<0.05). However, METH UTox+ subjects had significantly reduced proliferation to PHA (p<0.0005) and pathogen antigens (all p<0.04) compared to UTox–.

Conclusions: Our findings suggest that METH-use may activate and exhaust the immune system. Furthermore, METH might reduce the immune response to reactivating or invading pathogens leading to a loss of control of CMV and HIV replication, as suggested by an increase in CMV and HIV seminal shedding in the genital tract. Future studies should consider METH-use as a potential modulator of T-cell responses.

THURSDAY, FEBRUARY 26, 2015

Session P-C14 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Dissecting Pathogenesis Through In Vivo Studies

331 A Random Forest Approach to Define Immunological Thresholds for CD4 Recovery in HIV-Treated Individuals

Josué Pérez-Santiago[1]; **Marta Massanella**[1]; Dan Ouchi[2]; Elisabet Gómez[2]; Cecilia Cabrera[2]; Bonaventura Clotet[3]; Eugenia Negredo[3]; Julià Blanco[2]

[1]University of California San Diego, La Jolla, CA, US; [2]IrsiCaixa Institute for AIDS Research, Badalona, Spain; [3]LIuita Contra la Sida Foundation, Germans Trias i Pujol University Hospital, Badalona, Spain

Background: The failure to increase CD4 T-cell counts in some ART-suppressed patients has been related to low CD4 T-cell production, high activation and cell death. While some clinical data indicate that low CD4 threshold (i.e. 200 CD4 cells/μL) may have strong impact on survival, the lack of an accepted standard definition of immune recovery hamper a proper clinical follow up and has led to discrepant results among different studies. Our aim is to use a supervised machine learning approach to evaluate different clinical definitions of immune recovery.

Methods: In a cross-sectional, case-control study, 185 participants on suppressive ART (<50 copies/mL for ≥2 years) were evaluated for CD4 T-cell production, immune activation markers, soluble CD14, cell death, clinical and demographical variables. We use random forest classification (R statistical software) to investigate different definitions of immune recovery based on 1) CD4 T-cell counts (using cut-off values ranging from 250 to 600 cells/μL) and 2) CD4 T-cell increase from CD4 nadir value (Delta CD4, using values ranging from 50 to 500 cell/μL). Patients below or above the indicated values were considered as discordant, or concordant respectively.

Results: Among all CD4 cut-off definitions, 400 cells/μL cut-off segregated best concordant vs. discordant individuals with a balanced accuracy of 85%, specificity of 87% and sensitivity of 83%. Most important variables included intrinsic and total apoptosis of CD4 T cells, CD4 nadir, and the frequency of Fas$^+$HLA-DR$^+$ CD4 T cells. When Delta CD4 definitions were used, the best classifier was obtained with an increase of 300 CD4 cells/μl with a balanced accuracy of 79%, specificity of 77% and sensitivity of 81%. Surprisingly, the most important variable for delta CD4 classifications was CD8 absolute count, along with CD4 cell death (total, intrinsic apoptosis and necrosis) and CD4 activation, while CD4 nadir was not an essential defining parameter. Variables previously related to discordance (such as thymic production, time on ART or CD8 T-cell activation) did not show significant importance for any classification.

Conclusions: The 400 cell/μl cut-off definition classified better discordant and concordant patients than Delta CD4 classifications. As expected cut-off classification was strongly associated with destruction and activation of CD4 T cells. However, the gain of CD4 T cells is strikingly associated to CD8 absolute counts, corroborating the use of CD4/CD8 ratio as a measure of immune recovery.

332 Disease Progression in HIV Controllers; Uptake and Outcome of Antiretroviral Therapy

Jane R. Deayton[1]; Katherine C. Groves[2]; David F. Bibby[2]; Duncan A. Clark[2]; Iain Reeves[3]; Jane Anderson[3]; Chloe M. Orkin[4]; Eithne O'Sullivan[1]; Áine McKnight[1]

[1]Barts and the London, Que, London, United Kingdom; [2]Barts Health NHS Trust, London, United Kingdom; [3]Homerton University Hospital NHS Foundation Trust, London, United Kingdom; [4]Barts Health NHS Trust, London, United Kingdom

Background: We have previously reported a cohort of 86 HIV-1 "controllers" and defined a subset, "discord controllers (DC)" with low or declining CD4 counts (<450) despite control of plasma viral RNA. We showed that DCs are distinct both clinical and immunologically, having depletion of naïve CD4 cells and higher activation in all CD4 subsets compared with typical controllers (TC). Data are scarce on clinical management and outcome of controllers so we undertook a follow-up study of the cohort.

Methods: HIV controllers recruited into the prospective cohort were designated DC or TC depending on the geometric mean titre of the last 3 CD4 counts. Controls were HIV non-controllers and uninfected individuals. Baseline HIV-1 DNA load in peripheral blood mononuclear cells was determined by quantitative PCR and expressed as per cell equivalent.

Results: 18 DCs were recruited; 2 are lost to follow-up. DCs had higher DNA loads (13-1529, median 601 copies/10^6 CD4 cells) compared to TCs (0-755, median 87) (p=0.002) and were similar to those in non-controllers (27-2188, median 852). Ten DCs had received 12-66 (median 42) months of antiretroviral therapy (ART). RNA loads were 85-19837 (median 796) at ART initiation and all became undetectable on therapy. However, CD4 gain was modest; from baseline 163-308 (median 272), CD4 change was -25 – +318 (median +130) over follow-up. Those with lower nadir CD4 had lowest CD4 gain despite extended ART. Of 6 ART naïve patients, only one remained undetectable. CD4 counts in the naïve patients were unexpectedly low at 217-464 (median 304). Of note, 5 patients had declined to start ART despite low and declining CD4 counts.

Conclusions: The significantly higher DNA loads in the DC group suggest productive ongoing HIV-1 replication and are compatible with increased immune activation, poor clinical outcomes and sub-optimal CD4 response to ART as described in this, and other, controller cohorts. Initiation of ART occurred late in DCs (some declined treatment), suggesting that both clinicians and patients may feel falsely reassured by low RNA loads in the face of low CD4 counts. These results suggest that controllers may benefit from earlier ART and that clinicians should remain vigilant to this despite low or undetectable RNA loads. In addition, DNA load may be a better marker of viral replication and disease progression than RNA load and may identify controllers in whom early ART is indicated. Ongoing longitudinal follow-up of this cohort is planned.

333 Immunological and Virological Progression in HIV Controllers

Nicolas Noel[1]; Nathalie Lerolle[1]; Camille Lecuroux[2]; Cécile Goujard[1]; Alain Venet[2]; Asier Sáez-Cirión[3]; Véronique Avettand-Fenoel[4]; Laurence Meyer[5]; Faroudy Boufassa[5]; Olivier Lambotte[1]
ANRS CO21/CODEX Study Group

[1]APHP, Service de Médecine Interne et Immunologie Clinique, Hôpital Bicêtre, Le Kremlin-Bicêtre, France, Le Kremlin Bicêtre, France; [2]Inserm U1012, Régulation de la Réponse Immune, Infection VIH1 et Autoimmunité, Le Kremlin Bicêtre, France; [3]Institut Pasteur, Unité de Régulation des Infections Rétrovirales, Paris, France; [4]APHP, Service de Virologie, Hôpital Necker – Enfants Malades, Paris, France; [5]Inserm U1018, Centre de Recherche en Epidémiologie et Santé des Populations, Université Paris Sud, Le Kremlin-Bicêtre, France

Background: HIV controllers (HICs) display spontaneous long-term control of HIV replication. Some HICs show a decline in their CD4 T cell count or lose the ability to control the virus. The aim of this study was to investigate the rate and determinants of immunological and/or virological progressions in a large cohort of HICs.

Methods: HICs from the French ANRS CO21/CODEX study are ART-naive HIV-1-infected patients diagnosed for > 5 years with 5 last consecutive HIV viral loads (VL) < 400 copies/mL. Immunological progression during follow-up was suspected if CD4 T cell count fell < 350/mm^3 or declined by more than 200/mm^3 from a last CD4 count ≤ 600/mm^3. Viral progression was suspected if HIV VL rose > 2000 copies/ml. The events of immunological and virological were confirmed if similar CD4 counts or VL were found on a consecutive measurement. Clinical characteristics were analysed at inclusion in the cohort and prior to the event. Immune activation and inflammatory parameters (% of HLADR+CD38+ T cells, IP10 levels), ultrasensitive HIV VL and total HIV DNA were compared using non parametric tests with the non-progressor HICs.

Results: Out of 217 patients followed in the cohort between 2009 and 2013, 37 patients experienced at least one suspicion of progression. Progression was confirmed in 15 patients (immunological progression, n=10; viral progression, n=5). Compared with non-progressor HICs, viral progressors (VP) were enrolled younger (p<0.01). No differences in terms of HLA B57 status or HCV coinfection were observed. Unprotected sexual intercourse and sexually transmitted infections were reported in the recent history of some HICs, but not more frequently in progressors. Relative to non-progressors, immunological progressors HICs had lower CD4 T cell nadir (median (IQR): 292 (236-373) vs. 516 (412-681)/mm^3, p<0.001), as well as the CD4 count at inclusion, and viral progressors had higher ultrasensitive HIV RNA levels at inclusion (i.e., 1-2 years before progression) (p<0.01 for all). Interestingly, CD8 T cell activation and IP10 levels at inclusion in immunological progressors were significantly higher than in non-progressors (p<0.001), almost as elevated as observed in viremic non HICs patients.

Conclusions: CD4 T cell nadir, level of residual HIV replication and levels of basal immune activation seem major determinants to progression in HICs, and should be considered in order to adjust their follow-up and optimize the timing of cART initiation.

334 HIV Replication History Is Associated With Plasma IL-7 Levels in Aviremic Youths

Daniel Scott-Algara[1]; Jerome Lechenadec[2]; Josiane Warszawski[2]; Thomas Montange[1]; Jean-Paul Viard[3]; Catherine Dollfus[3]; Véronique Avettand-Fenoel[4]; Christine Rouzioux[4]; Stéphane Blanche[3]; **Florence Buseyne**[1]

[1]Institut Pasteur, Paris, France; [2]Inserm, Le Kremlin-Bicêtre, France; [3]AP-HP, Paris, France; [4]Université Paris Descartes, Paris, France

Background: IInterleukin-7 (IL-7) is a key molecule regulating thymopoiesis and peripheral T-lymphocyte proliferation. We previously reported that thymopoiesis was maintained and that naive T cells had high levels of IL-7 high-affinity receptor in both viremic and aviremic youths infected with HIV-1 during the perinatal period. Plasma IL-7 levels were associated with CD4 T-cell count only in viremic patients. Here, we focused on aviremic patients, investigating the factors of HIV disease history associated with plasma IL-7.

Methods: The ANRS-EP38-IMMIP study comprised youths between the ages of 15 and 24 years that had been perinatally infected with HIV and were living in France. Fifty-eight treated patients with < 80 copies of HIV RNA/ml at the time of the study were included in the analysis. T-cell subsets were quantified by flow cytometry. Plasma IL-7 was quantified by ELISA. Univariate and multivariate linear regression analyses were performed.

Results: : Median (interquartile range) plasma IL-7 concentration at the time of the study was 3.9 (2.7-4.6) pg/ml. Higher IL-7 levels were associated with higher cumulative viremia over the last 10 years and higher levels of cell-associated HIV DNA (coefficient [95% CI]: 1.43 [0.20; 2.65] per 10000 days x $\log_{10}$ HIV RNA copies/ml, P=0.02, and 0.77 [-0.03; 1.59] per $\log_{10}$ HIV DNA copies/10^6 PBMCs, P=0.06, respectively). The weak negative correlation between IL-7 levels and CD4 T-cell count was not significant (-0.13 [-0.30; 0.04] per 100 cells/μl, P=0.13). Neither nadir CD4 T-cell percentage nor duration of severe immunosuppression were correlated with IL-7 levels (-0.11 [0.71; 0.49] per 100 cells/μl, P=0.72 and -0.05 [-0.10; 0.20] per year, P=0.53). IL-7 levels were not associated with sex, ethnicity, previous CDC stage C events, HIV-1 subtype or tropism. In multivariate analysis, IL-7 levels were significantly associated with cumulative viremia only (1.26 [0.02; 1.46] per 10000 days x $\log_{10}$ HIV RNA copies/ml, P=0.05). In addition, higher IL-7 levels were associated with lower central-memory CD4 percentage and weaker CD127 expression on this CD4 T-cell subset.

Conclusions: In youths with suppressed HIV viremia, plasma IL-7 levels were associated with exposure to viral replication over the previous 10 years. A similar association was reported with the naive CD4 T cells, consistent with a major impact of past HIV replication on current naive CD4 T-cell homeostasis in patients with perinatally acquired HIV infection.

335 Enhanced Immune Reconstitution With Initiation of ART at HIV-1 Seroconversion (PHI)

Sabine I. Kinloch[1]; Colette Smith[1]; Kwong Tsz-Shan[2]; Jayne Ellis[2]; Margaret Johnson[2]

[1]University College London, London, United Kingdom; [2]Royal Free London NHS Foundation Trust, London, United Kingdom

Background: Early ART initiation has been shown recently to delay the time to AIDS, strengthening the case for early intervention. It is unclear whether immune reconstitution in particular, CD4/CD8 ratio, is enhanced with intervention at Primary HIV Infection (PHI).

Methods: We undertook a retrospective study of a PHI cohort (ART initiation ≤3 months from PHI) from a single center (Royal Free Hospital, London, UK) who had received ≥5 years of continuous ART. The group were compared to a cohort of individuals who started ART at the same center during chronic infection (CI; ≥1 year after diagnosis) with a pre-ART CD4 count>350 cells/mm^3 and who also received ≥5 years(y) of continuous ART. Median CD4 count, CD4%, CD4/CD8 ratio and presence of optimal immune reconstitution (OIR) (CD4≥800 cells/mm^3 or CD4%≥40% or CD4/CD8 ratio≥1) were assessed and compared in the 2 cohorts at 1, 5 and 10y post-ART initiation by considering the measure that occurred closest to the time-point, provided it was ≤6 months. Time to normalization of CD4/CD8 ratio to ≥1 was also assessed using Kaplan-Meier methods.

Results: 37 PHI and 115 CI individuals were included. Median age at time of HIV diagnosis was 34 vs 32 years in the PHI and CI cohorts, respectively. 35 (95%) vs 32 (87%) were male and 32 (87%) vs 84 (73%) were MSM. Median pre-ART nadir CD4 count, CD4% and CD4/CD8 ratios were: 417 vs 313 cells/mm^3; 18% vs 16%, and 0.30 vs 0.29, respectively. Median maximum pre-ART VL were 511,000 (range 3,400, >1.000,000 vs 278,022 (2593, >750,000) copies/mL, respectively.

After 1, 5 and 10 y of ART, median CD4 count, CD4% and CD4/CD8 ratio were significantly higher in the PHI compared to the CI group across all time-points (Table). Similarly, OIR was more common in the PHI group at all time-points. The kinetics of CD4/CD8 ratio showed that the median time to achieving CD4/CD8 ratio≥1 was 36 (95% CI 16-63) weeks in the PHI cohort and 187 (127-204) weeks in the CI cohort (p<0.0001; log rank test).

– Comparison of immunological reconstitution in individuals who start ART during primary infection (PHI) vs in Chronic Infection (CI)

me nce art RT	Median CD4 count (cells/mm^3)			Median CD4%			Median CD4:CD8 ratio			Presence of OIR*		
	PHI	CI	P-value	PHI	CI	P-value	PHI	CI	P-value	PHI	CI	P-value
Year	743	800	<0.0001	35	26	<0.0001	0.95	0.52	<0.0001	51% (19/37)	25% (39/153)	0.002
	850	779	0.005	39	33	<0.0001	1.05	0.78	<0.0001	73% (27/37)	46% (73/158)	0.003
ears												
)	966	874	0.02	38	33	0.01	1.09	0.85	0.04	85% (23/27)	53% (38/72)	0.003
ears												

* OIR=optimal immune reconstitution defined by CD4 count =800 cells/mm^3 or CD4% = 40% or CD4:CD8 ratio = 1.00
# 27 patients in PHI cohort had more than ten years of follow-up since treatment initiation

Conclusions: Immunological response to ART in this cohort was excellent, with high median CD4 counts after 10 y of ART. Despite this, ART initiation within 3 months of PHI shows improved immune reconstitution in terms of CD4 T cell count and CD4/CD8 ratio, when compared to a CI cohort initiating ART without severe immunosuppression,. These differences persisted even after 10 years of ART, suggesting damage to the immune system during the early stages of HIV infection can have long-term consequences.

336 cART-Driven Recovery of Immune Function Preferentially Targeting CXCR4-Tropic HIV-1

Joëlle Bader[1]; Martin Däumer[2]; Jürg Böni[4]; Meri Gorgievski[3]; Thomas Klimkait[1]
The Swiss HIV Cohort Study

[1]University of Basel, Basel, Switzerland; [2]Institute for Immunogenetics, Kaiserslautern, Germany; [3]University of Berne, Berne, Switzerland; [4]Swiss National Center for Retroviruses, Zürich, Switzerland

Background: It has been shown that CXCR4-tropic HIV is better neutralized by the immune system than CCR5-tropic variants. Reasons therefore might be the less glycosylated envelope on CXCR4-tropic viruses and the antibody binding due to less steric hindrance. We hypothesize that CXCR4-tropic variants should be better eliminated by a competent immune system generated through efficient cART. Aim of this study was to monitor the frequency of CXCR4-tropic viruses through restoration of the immune system by cART.

Methods: Seventeen patients in the Swiss HIV Cohort Study were followed yearly after virological suppression by tropism testing. All patients were fully suppressed throughout study time and showed good CD4 T cell restoration (>250 cell/mm^3 in 3 years) after cART initiation. For eight we included also three consecutive time points before cART. Frequency of CXCR4-tropic variants was analyzed by Illumina Miseq sequencing (FPR 3.5%, R5 < 2% X4).

Results: Ten patients (59%) had only CCR5-tropic viruses after cART initiation, which stayed CCR5-tropic during follow-up. Of the seven remaining patients with CXCR4-tropic HIV, four (57%) showed decreasing frequencies of CXCR4-tropic variants during therapy. For 15 of the 17 patients we could perform proviral load testing on all time points, four (27%) showed increased proviral loads under therapy. Interestingly, all patients with increasing CXCR4-tropic frequencies had also increasing proviral loads. For four of the seven patients with CXCR4-tropism after therapy we could include tropism data before cART initiation, which showed that all of them had increasing frequencies of CXCR4-tropic viruses with time and without therapy. Two patients of them had even an R5 tropism three years before cART initiation.

Conclusions: We identified a decrease in the frequency of CXCR4-tropic HIV variants under successful cART in the majority of patients in our study. An increase under therapy strictly correlated with increasing proviral loads. We suggest that CXCR4-tropic variants can be better eliminated by the recovering immune system under cART and similarly in early stages of the infection, when immune surveillance is still largely intact. On contrast, weakening of the immune system leads to an increase in CXCR4-tropic viruses. Therefore early therapy initiation and maintaining of an effective immune state might help to better control CXCR4-tropic HIV variants.

337 Repeated injections of r-hIL-7 in HIV Patients receiving ART in INSPIRE 2 & 3 trials

Rodolphe Thiebaut[1]; Ana Jarne[1]; Jean-Pierre Routy[2]; Irini Sereti[3]; Margaret A. Fischl[4]; Prudence Ive[5]; Roberto Speck[6]; Giuseppe Tambussi[7]; Yves Lévy[8]; Michael M Lederman[9]
on behalf of Inspire 2 and Inspire 3 study groups

[1]Bordeaux University, Bordeaux, France; [2]McGill University, Montreal, Canada; [3]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US; [4]University of Miami, Miami, FL, US; [5]Wits Health consortium, Johannesburg, South Africa; [6]University Hospital Zurich, Zurich, Switzerland; [7]San Raffaele Scientific Institute, Milano, Italy; [8]INSERM, Paris, France; [9]Case Western Reserve University, Cleveland, OH, US

Background: Phase I/II studies in HIV-infected patients receiving ART have shown that administration of 3 weekly subcutaneous (s/c) injections of Recombinant Human Interleukin 7 (r-hIL-7) is safe and increase numbers of both naive and memory CD4 and CD8 T cells. Here, we report the pooled data from two phase II trials evaluating the effect of repeated cycles of r-hIL-7 with the objective of restoring and maintaining CD4 T cell count over 500 cells/μL.

Methods: INSPIRE 2 was a single arm trial conducted in US and Canada. INSPIRE 3 was a two arm trial with 3:1 randomization to rhIL-7 vs. control conducted in Europe and South Africa. Participants had to be receiving ART with plasma HIV-RNA<50 copies/mL and CD4 T-cell count between 101-400 cells/μL. Patients with chronic hepatitis B or C co-infection or active infections were excluded. R-hIL-7 was administered at 20 μg/kg, in 3 weekly s/c injections per cycle. A repeat cycle was administered if, at any quarterly evaluation, CD4 Tcells fell below 550 cells/μL. In INSPIRE 3, participants randomized to the control arm crossed to receive r-hIL-7 if CD4 cells were below 500 cells/μL at 12 months.

Results: 111 patients were included: 23 in INSPIRE 2 and 88 in INSPIRE 3 including 24 in the control arm. They received one (107), two (74), three (14) or four r-hIL-7 cycles (1) over a median follow-up of 23 months. R-hIL-7 was well tolerated. Four grade 4 events were observed including one asymptomatic ALT elevation. After the induction cycle in INSPIRE 2 and 3 respectively, 6% and 17% developed binding antibodies against IL-7 (neutralizing in 0% and 1%). After the second cycle binding antibodies developed in 82% and 77% (neutralising in 38% and 37%) without impact on the CD4 response. 13% and 17% of patients experienced at any time HIV RNA > 200 copies/mL in INSPIRE 2 and 3, respectively. HIV DNA per CD4 T cells and per PBMC was stable over follow up. The first cycle led to a substantial increase of CD4 T cells, mainly naïve and central memory without expansion of Treg cells. Half the patients spent more than 63% of their follow-up with more than 500 CD4 T cells/μL. The baseline CD4 level was a strong predictor of the probability of staying above 500 CD4 T cells/μL (HR=2.2, p<.0001) whereas there was no difference between the repeated cycles (HR=.99, p=.96).

Conclusions: Repeated cycles of r-hIL-7 were well tolerated and achieved sustained immune restoration over 500 CD4 T cells/μL in the majority of study participants.

338 CRF19_cpx Is an Evolutionary Fit HIV-1 Variant Exclusively Associated With Rapid Progression to AIDS in Cuba

Vivian Kouri[2]; Ricardo Khouri[1]; Yoan Alemán[2]; Yeissel Abrahantes[2]; Nico Pfeifer[3]; Andrea-Clemencia Pineda-Peña[4]; Jorge Pérez[2]; Lissette Pérez[2]; Kristel Van Laethem[4]; **Anne-Mieke Vandamme**[4]
[1]Fundação Oswaldo Cruz, Salvador, Brazil; [2]Instituto Pedro Kouri, Havana, Cuba; [3]Max Planck Institute for Informatics, Saarbrucken, Germany; [4]Katholieke Universiteit Leuven, Leuven, Belgium

Background: Clinicians reported an increasing trend of rapid progression (RP) (AIDS within 3 years of infection) in Cuba.

Methods: Recently infected patients were prospectively sampled, 52 RP at AIDS diagnosis (AIDS-RP) and 21 without AIDS in the same time frame (non-AIDS). 22 patients were sampled at AIDS diagnosis (chronic-AIDS) retrospectively assessed as >3 years infected. Clinical, demographic, virological, epidemiological and immunological data were collected. Pol and env sequences were used for subtyping, transmission cluster analysis, and prediction of resistance, coreceptor use and evolutionary fitness. Host, immunological and viral predictors of RP were explored through data mining.

Results: Subtyping revealed 25 subtype B strains, 6 C, 7 CRF18_cpx, 9 CRF19_cpx, 29 BG-recombinants and other subtypes/URFs. All CRF19 were AIDS-RP. Data mining identified CRF19, oral candidiasis and RANTES levels as strongest predictors of AIDS-RP. CRF19 was more frequently associated with CXCR4 coreceptor use, higher fitness scores in the protease region, and higher viral load at diagnosis.

Patient characteristics Clinical, immunological and virological markers for the non-AIDS, chronic-AIDS and AIDS-RP groups

1) Patient characteristics at HIV diagnosis for the non-AIDS, chronic-AIDS and AIDS-RP groups.				
	non-AIDS (N=21)	**Chronic-AIDS (N=22)**	**AIDS-RP (N=52)**	**p value**
Last negative HIV test before HIV diagnosis (months)	22.0 (10.5-25.0) (N=21)	22.0 (12.0-24.0) (N=22)	14.0 (5.3-23.5) (N=52)	0.17
Log VL at HIV diagnosis (RNA copies/ml plasma)	<1.7 (<1.7-3.5) (N=12)	3.2 (<1.7-3.9) (N=8)	4.8 (4.1-5.4) (N=41)	**<0.0001**
CD4 count at HIV diagnosis (cells per μl blood)	577 (441-815) (N=20)	522 (374-782) (N=22)	276 (152-386) (N=49)	**<0.0001**
Anal sex (as reported by both males and females of various sexual orientation)	80.0% (16/20)	54.6% (12/22)	50.0% (25/50)	**0.031**
Always condom use after diagnosis	45.0% (9/20)	45.5% (10/22)	19.6% (10/51)	**0.016**
Sexual orientation				
Heterosexual	20.0% (4/20)	36.4% (8/22)	49.0% (25/51)	**0.023**
Homosexual	65.0% (13/20)	45.5% (10/22)	41.2% (21/51)	0.087
Bisexual	15.0% (3/20)	18.2% (4/22)	9.8% (5/51)	0.44
2) Clinical, immunological and virological markers at sampling for the three studied groups.				
	non-AIDS (N=21)	**Chronic-AIDS (N=22)**	**AIDS-RP (N=52)**	**p value**
Years elapsed from HIV seroconversion to sampling	1.75 (1.25-2.33) (21)	9.82 (7.97-12.06) (22)	1.40 (0.79-2.16) (52)	-
Log VL at sampling (RNA copies/ml plasma)	3.7 (3.0-4.3) (N=20)	4.7 (4.2-5.4) (N=22)	4.7 (4.0-5.4) (N=47)	**0.0012**
CD4 count at sampling (cells per μl blood)	501 (408-641) (N=17)	212 (113-266) (N=17)	189 (91-225) (N=51)	**<0.0001**
RANTES/CCL5 (pg/ml)	944 (719-1184) (N=18)	1291 (932-1430) (N=21)	1398 (1103-1630) (N=47)	**0.00060**
Co-infections (proportion)				
Oral Candidiasis	4.8% (1/21)	0.0% (0/22)	23.1% (12/52)	**0.013**
HIV subtypes (proportion)				
Subtype B	38.1% (8/21)	40.9% (9/22)	17.3% (9/52)	**0.034**
Subtype C	0.0% (0/21)	4.6% (1/22)	9.6% (5/52)	0.11
CRF18_cpx	9.5% (2/21)	9.1% (2/22)	5.8% (3/52)	0.54
CRF19_cpx	0.0% (0/21)	0.0% (0/22)	17.3% (9/52)	**0.0090**
CRF20,23,24_BG	33.3% (7/21)	22.7% (5/22)	32.7% (17/52)	0.88
Co-receptor use				
X4 (FPR<5%)	0.0% (0/12)	17.7% (3/17)	15.8% (6/38)	0.32
X4-R5X4 (5%≤FPR≤20%)	33.3% (4/12)	29.5% (5/17)	42.1% (16/38)	0.73
R5(FPR>20%)	66.7% (8/12)	52.9% (9/17)	42.1% (16/38)	0.24

1) Patient characteristics at HIV diagnosis for the non-AIDS, chronic-AIDS and AIDS-RP groups. 2) Clinical, immunological and virological markers at sampling for the three studied groups. TDR (transmitted drug resistance): NRTI resistance mutations M41L, F116Y/T215S/K219Q, M41L/T215D and D67N/T215S/K219Q; NNRTI resistance mutations twice K103N and PI resistance mutations N88DN and M46L. Data are expressed as median values with interquartile ranges, or as proportion (%) with number of patients between brackets. Statistical differences between groups were tested using Kruskal-Wallis or Chi-square test for trend. Results were considered significant at p-value<0.05 (displayed in bold). N = number of patients.

Conclusions: CRF19 is a recombinant of subtype D (C-part of Gag,PR, RT and nef), subtype A (N-part of Gag, Integrase, Env) and subtype G (Vif, Vpr, Vpu and C-part of Env). Since subtypes D and A have been associated with respectively faster and slower disease progression, our findings might indicate a fit PR driving high viral load, which in combination

with coinfections may boost RANTES levels and thus CXCR4 use, potentially explaining the fast progression. We propose that CRF19 is evolutionary very fit and causing rapid progression to AIDS in many newly infected patients in Cuba.

TUESDAY, FEBRUARY 24, 2015

Session P-E1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

The Effect of HIV Infection on B Cells

339 Acute HIV-1 Infection Is Associated With Rapid Changes in B-Cell Subsets and Levels of CXCL13

Jenniffer K. Maroa[1]; Anne-Sophie Dugust[2]; Zelda Euler[2]; Yathisha Ramlakhan[1]; Krista Dong[3]; Bruce Walker[2]; Thumbi Ndung'u[4]; Galit Alter[2]

[1]University of KwaZulu-Natal, Durban, South Africa; [2]Ragon Institute of MIT, MGH and Harvard, Boston, MA, US; [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [4]HIV Pathogenesis Programme, Durban, South Africa

Background: HIV chronic infection (CI) is characterized by perturbations in B cell homeostasis, phenotype and function. There are limited data describing B cell dynamics during HIV acute infection (AI). Characterizing B cell subsets during AI might help define signatures that shape the humoral response in HIV infection.

Methods: Eleven women who became HIV-1 infected during a longitudinal follow-up study in Durban, South Africa were analyzed. Samples were analyzed at baseline (pre-infection) and weeks 1, 2, 4 and 12 post detection of HIV RNA. Multicolor flow cytometry was used to identify B cell subsets based on expression of CD21CD27 on live CD19+ lymphocytes and defined as follows; activated memory (AM) CD27+CD21-, resting memory (RM) CD27+ CD21+, naïve cells (N) CD27-CD21+, tissue-like memory (TLM) CD27-CD21- and plasmablasts (PBs) CD27+CD38+ cells. Evolution of HIV-specific antibodies and changes in CXCL13 levels were determined by ELISA

Results: Compared to a baseline sample, we observed rapid and significant expansion of TLM cells post HIV infection (PI); 1week ($p = 0.0003$), 2 weeks ($p = 0.0018$), 1 month ($p = 0.046$) and 3 months ($p = 0.043$). In contrast, RM cells were significantly lower throughout AI compared to baseline; 1week ($p = 0.0007$), 2 weeks ($p = 0.016$), 1 month ($p = 0.019$) and 3 months ($p = 0.018$). We observed significant expansion of AM cells at 2 weeks and 1 month ($p = 0.008$, $p = 0.009$ respectively) followed by contraction by 3 months ($p = 0.260$) PI. Peripheral blood PBs peaked by a median of 17 days (range 7-32 days) PI. Changes in B cell subsets were driven by the increase in viral loads. Levels of CXCL13 a chemokine critical for B cell homing to the germinal centers also increased over time in the first 3 months.

Conclusions: Perturbations in B cell subsets and CXCL13 levels occurs immediately following HIV-1 infection and this may therefore determine the subsequent development of anti-HIV antibodies.

340 Bone Marrow Plasma Cells Dictate Serum HIV-Specific Antibodies in Chronic Viremia

Jairo Mauricio Montezuma-Rusca[1]; **Olivia R. Fankuchen**[1]; Lela Kardava[1]; Clarisa M. Buckner[1]; Aaron Louie[1]; Yuxing Li[2]; Tae Wook Chun[1]; Katherine R. Calvo[3]; Susan Moir[1]; Anthony S. Fauci[1]

[1]NIAID/NIH, Bethesda, MD, US; [2]University of Maryland, Rockville, MD, US; [3]NIH Clinical Center, Bethesda, MD, US

Background: Screening for HIV-neutralizing antibody activity in the serum or plasma has been the starting point for the isolation of several potent and broadly neutralizing antibodies to HIV from peripheral blood B cells of infected individuals. Despite the success of this approach, little is known regarding the cells that produce the antibodies detected in the serum. To gain a better understanding of the cellular source of circulating antibodies, we investigated two possible sources, the bone marrow and peripheral blood, of chronically HIV-viremic individuals.

Methods: Bone marrow biopsies and peripheral blood samples were obtained from eight chronically HIV-viremic individuals and bone marrow cells were obtained from eight healthy HIV-negative controls. Written informed consent was provided. Immunophenotyping was performed on cell suspensions using B-cell subset-defining markers. A biotinylated HIV envelope gp140 probe was used to measure HIV-specific antibodies in serum (via ELISA), HIV-specific plasmablasts (via ELISPOT) or memory B cells (via flow cytometry) in blood, and HIV-specific plasma cells in bone marrow (via ELISPOT).

Results: Compared to HIV-negative counterparts, the bone marrow aspirates of the HIV-infected participants contained increased frequencies of plasma cells and B cell precursors (namely preB-I and preB-II), and decreased frequencies of mature B cells. Levels of HIV-specific antibodies measured in serum were compared to corresponding frequencies of antibody-secreting or -binding cells measured in the bone marrow (plasma cells) and the blood (plasmablasts and memory B cells). A strong correlation was observed between HIV-specific antibodies in serum and the HIV-specific bone marrow-derived plasma cells, but not the plasmablasts or memory B cells from blood.

Conclusions: Increased frequencies of plasma cells in the bone marrow are consistent with known hallmarks of HIV infection, namely hypergammaglobulinemia and increased frequencies of peripheral blood plasmablasts. These findings demonstrate that despite HIV-induced phenotypic and functional B-cell dysregulation in the peripheral blood and secondary lymphoid tissues, bone marrow plasma cells remain a primary source for circulating HIV-specific antibodies in HIV-infected individuals.

341 Reduced Expression of Blimp-1 on Memory B Cells in Patients with HIV-1 Infection

Claudia Beisel; Ilona Toth; Jan van Lunzen; Julian Schulze zur Wiesch

University Hospital Hamburg-Eppendorf, Hamburg, Germany

Background: Blimp-1 has long been recognized as master regulator for B cell development and has additionally been recognized as important rheostat, balancing effector function and T cell exhaustion. Although several studies described Blimp-1 in the context of T cell exhaustion in viral infections, the role of Blimp-1 was first and primarily defined as a "master regulator" of terminal B cell development. Blimp-1 attenuates the expression of many transcription factors, thereby inhibiting B cell proliferation and B cell receptor mediated activation while promoting immunoglobulin secretion and plasma cell differentiation. Here, we present novel data describing the expression pattern of Blimp-1 in different B cell memory subsets in a cohort of viremic and treated HIV-1 patients.

Methods: The expression of Blimp-1 in different B cell memory subsets was analyzed by flow cytometry in a cohort of 26 individuals, classified as healthy donors ($n = 7$), treatment naïve HIV-1 infected patients ($n = 9$) and HIV-1 infected patients under antiretroviral therapy (cART) ($n = 10$). B cell memory subsets were defined as activated memory B cells ($CD20^+/CD21^{lo}/CD27^{int}$), tissue like memory B cells ($CD20^+/CD21^{lo}/CD27^-$), resting memory B cells ($CD20^+/CD21^{hi}/CD27^{int}$) and naïve memory B cells ($CD20^+/CD21^{lo}/CD27^{lo}$).

Results: The expression of Blimp-1 on activated memory B cells was significantly down-regulated in patients with HIV-1 infection compared to healthy donors. Viremic, treatment naïve patients showed an even lower expression of Blimp-1 than patients on cART. The relative frequency of Ki67 on activated memory B cells directly correlated with HIV viral load ($p = 0.005$, $r_2 = 0.30$). Additionally, the relative frequency of Blimp-1 on activated memory B cells inversely correlated with HIV-1 viral loads and the relative frequency of Ki67+ activated memory B cells ($p = 0.026$, $r_2 = 0.62$; $p = 0.033$, $r_2 = 0.51$) (Figure 1).

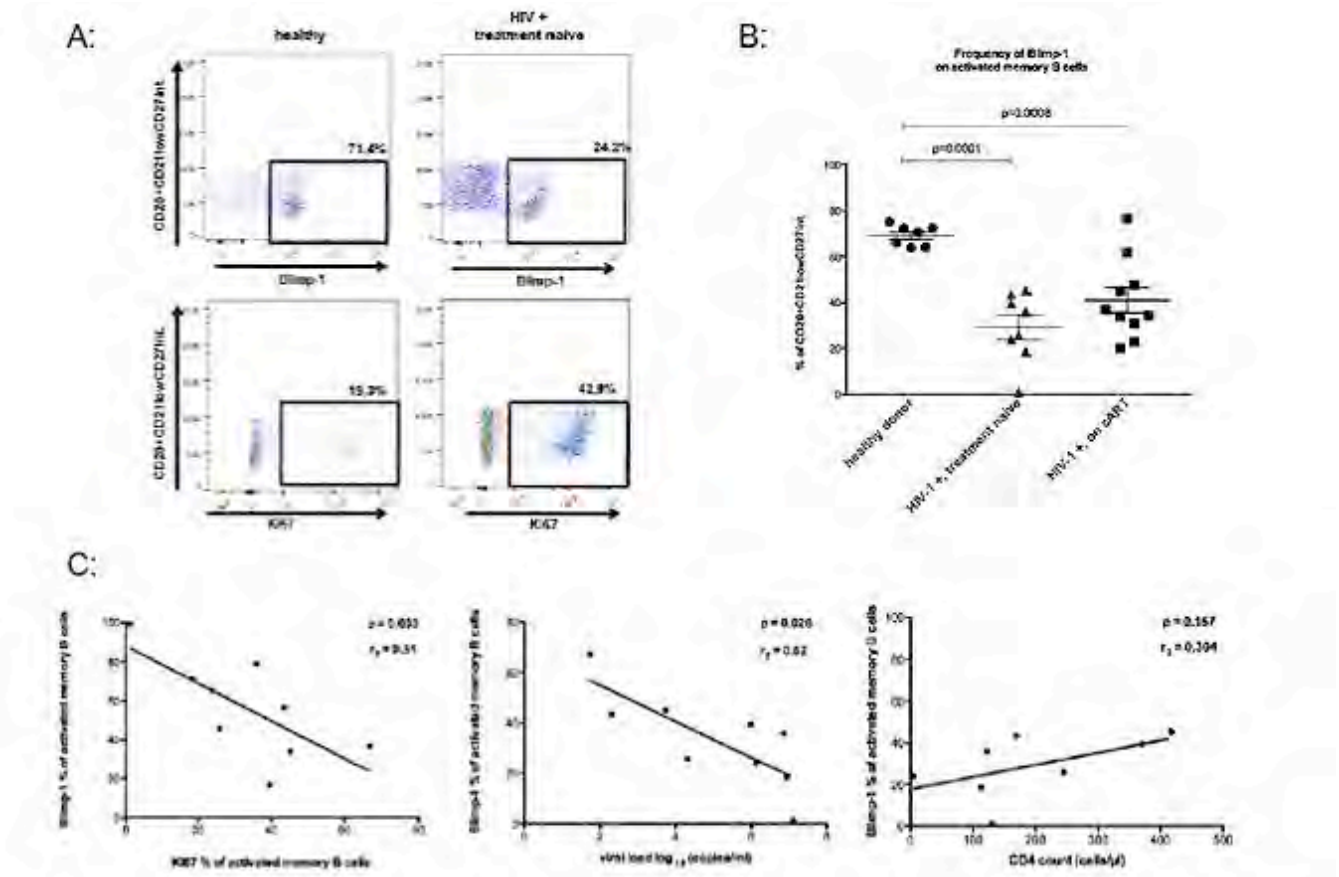


Figure 1: Blimp-1 expression is reduced in HIV-1 infected individuals on activated memory B cells and correlates inversely with HIV-1 viral load and Ki67 expression. (A) Representative fluorescence-activated cell sorter plot showing Blimp-1 and Ki67 expression on activated memory B cells ($CD20^+/CD21^{low}/CD27^{pos}$) in a HIV-1 seronegative individual (left) and a HIV-1 positive, treatment naïve individual (right). (B) Blimp-1 expression is significantly downregulated in HIV-1 positive individuals compared to HIV-1 seronegative individuals. Treatment naïve patients showed an even lower expression of Blimp-1 than patients on cART ($p = 0.0001$; $p = 0.008$). (C) Expression of Blimp-1 correlated inversely with Ki67 expression ($p = 0.033$, $r_2 = 0.51$) and with HIV-1 viral load ($p = 0.026$, $r_2 = 0.61$). Blimp-1 expression did not significantly correlate with CD4+ T cell count ($p = 0.157$, $r_2 = 0.304$).

Conclusions: To our knowledge, this alteration of Blimp-1 expression on activated memory B cells in patients with HIV-1 infection has not been described before. We propose to further investigate the hypothesis whether down-regulation of Blimp-1 expression on activated memory B cells in patients with HIV-1 infection leads to uncontrolled differentiation into antibody secreting cells and consequently to an impaired production of neutralizing antibodies that has been described in HIV infection.

342 Similar or Higher Memory Responses to Influenza Vaccination in Aviremic HIV-infected Patients on Antiretroviral Therapy

Zhenwu Luo; Lisa Martin; J. Michael Kilby; **Wei Jiang**
Medical University of South Carolina, Charleston, SC, US

Background: Potential for recovery of antigen (Ag)-specific B cell functioning after long-term antiretroviral therapy (ART) in HIV-infected patients is not fully understood.

Methods: We examined Ag-specific B cell responses to influenza (flu) vaccine in a cohort of 17 healthy controls and 28 ART-treated aviremic HIV+ patients who received vaccines last year and this year. Blood draws were taken at 0, 7, and 14 days after the latest vaccination. Number of Ag-specific antibody-secreting cells (ASC) were tested by ELISPOT in 0.5 million purified B cells at 0 and 7 days after vaccination. Flu vaccine-specific antibodies (IgM, IgG and IgA) were tested by ELISA in plasma. B cell apoptosis was assessed by flow cytometry.

Results: The median percentages of CD4+ T cell among total CD3+ T cells were 60.32% (IQR 49.64% - 69.32%) and

45.12% (IQR 34.63% - 57.3%), and the median percentages of total CD19+ B cells among all lymphocytes were 7.31% (IQR 5.0% - 9.2%) and 9.2% (6.4% - 11.1%) in controls and patients pre-vaccination, respectively. The frequencies of naïve (CD27-), memory B cells (CD27+) and plasma cells (CD27+CD138+) among B cells were similar in controls and patients pre-vaccination ($P > 0.05$). Ex vivo, apoptosis of naïve B and plasma cells, but not memory B cells, was higher in patients than controls pre-vaccination ($P < 0.05$, Mann Whitney U test). Numbers of flu-specific ASC (IgM and IgA) were low to undetectable at all time points. Number of flu-specific ASC (IgG) in 0.5 million B cells were similar in HIV+ patients and controls before vaccination and at 7 days after vaccination ($P > 0.05$). Ag-specific IgG responses were not related to CD4+ T cell counts at any time point in both controls and patients. Consistently, patients had similar or higher levels of flu-specific IgM, IgG and IgA in plasma pre-vaccination, 7 days and 14 days post-vaccination compared to controls.

Conclusions: Memory responses to influenza vaccination (TD antigen) are recovered in successful HIV virologic suppression after ART treatment even in patients with low CD4+ T cell counts, suggesting that recall responses are independent or much less dependent of CD4+ T cell help.

TUESDAY, FEBRUARY 24, 2015

Session P-E2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

The Envelope/Antibody Dynamic

343 Estimating and Visualizing HIV-1 Susceptibility to Broadly Neutralizing Antibodies

Anna Feldmann; Nico Pfeifer

Max Planck Institute for Informatics, Saarbrücken, Germany

Background: In HIV-1 treatment, clinicians still have to face drug-resistant viral strains, while the amount of available drugs and drug targets remains limited. Recently, combination therapy with broadly neutralizing antibodies (bNAbs) was introduced as a potential HIV-1 treatment that is capable to reduce viral load under detectable levels for up to 60 days in humanized mice and primates. However, similarly to HAART, the emergence of resistant strains is a major problem when selecting an efficient combination therapy of bNAbs for an individual patient. Prior to the administration of a bNAb combination therapy to a patient, it has to be ensured that the patient's viral strains are susceptible to the particular bNAb.

Methods: For seven different bNAbs we trained a classifier for each using support vector machines. The prediction models are able to determine the neutralization susceptibility of unseen viral strains to the specific bNAb based on the viral envelope sequence (Env). Different string kernels as well as the polynomial kernel and the Gaussian RBF kernel were tested by 10 times nested cross-validation. In addition, we introduce new visualization techniques (e.g., motif of most important residues) to increase model interpretability of non-linear classifiers.

Results: Among all considered kernels, the oligo string kernel performed best. High prediction performance could be traced back to learnt discriminant features that are supported by literature. State of the art performance of the classifiers can be seen in the table. For the V3-loop directed bNAbs the N-glycosylation site at position 332 was found as the most discriminant residue for neutralization susceptibility whereas position 334 confers neutralization resistance. The N-glycosylation site at position 160 was identified to be the most discriminant residue for the classifiers targeting the V1/V2 -loop indicating neutralization susceptibility. The classifiers for the CD4 binding site-directed bNAbs recognized different known binding sites to the CD4 molecule on the gp120 Env subunit to be associated with neutralization susceptibility of the viral strains. In addition to the already known epitopes, we also found other discriminant residues that might be interesting for follow-up structural studies.

Epitope	Antibody	AUC
V1/V2-Loop	PG9	0.67 (±0.03)
	PG16	0.71 (±0.03)
CD4bs	VRC01	0.71 (±0.03)
	VRC-PG04	0.69 (±0.04)
V3-Loop	PGT121	0.79 (±0.02)
	10-1074	0.84 (±0.02)
	10-996	0.81 (±0.03)

AUC (area under the curve) performance of each classifier assessed by 10 times 5-fold nested cross-validation.

Conclusions: The good classfier performances motivate their use in the selection of bNAb combination therapy. The robustness of the models implies that models with similar accuracy and interpretability can also be learnt for additional bNAbs.

344 Sequential SHIV-Env Clones With Neutralization Sensitivity for Breadth Development

Manxue Jia; Cecilia Cheng-Mayer; Xueling Wu

Aaron Diamond AIDS Research Center, New York, NY, US

Background: Neutralizing antibodies gradually increase in breadth in selected SHIV-infected rhesus macaques (RMs) and HIV-1-infected humans. However, the envelope (Env) clones that are responsible for the development of neutralization breadth have not been identified.

Methods: Because the SHIV-RM is the best available animal model for HIV-1 antibody studies, we screened 13 viremic RMs that were intra-rectally infected with the R5 clade B $SHIV_{SF162P3N}$ for neutralization activity against eight HIV-1 heterologous strains. Two animals, GB40 and FF69, were identified as containing the best neutralization breadths and titers. Using plasmas collected longitudinally from these animals, we tested four homologous Env clones derived from the $SHIV_{SF162P3N}$ inoculum and identified two sequential homologous neutralization activities (waves) prior to a third wave that cross-neutralized the tested HIV-1 strains. Based on the time when each wave appears, we selected time points for Env isolation. Full-length *env* sequences were obtained by single genome amplification, and representative *env* clones were tested for neutralization.

Results: From GB40, we obtained 116 *env* sequences and cloned 11 from week 2 (w2), w19 and w35 plasmas, and from the genomic DNA of w13 PBMC. The Env clone w2_1 is sensitive to plasmas from the wave 1 time points (w13 – w19). The Env clone w13_d13 is sensitive to time points between waves 1 and 2, and thus defined a new neutralization activity – wave 1b (w17 – w35). The other isolated GB40 Env clones are not particularly sensitive to wave 2 time points (~w45); therefore, the search for the specific Envs responsible for wave 2 continues. The isolated GB40 Env clones are sensitive to wave 3 time points (w54 and after) when heterologous neutralization is evident. From FF69, we thus far obtained 21 *env* sequences from the peak viremia (w2 plasma) and cloned two major variants, w2_17 and w2_27. Both variants are sensitive to wave 1 time points (w8 – w12) in this animal.

Conclusions: From two $SHIV_{SF162P3N}$-infected RMs, we identified 2-3 sequential waves of homologous responses before the appearance of the heterologous neutralization activity. Examination of sequential Env clones from these animals identified specific Envs with neutralization sensitivity to temporal plasmas in which neutralization specificity gradually broadens. The identification of these Env clones is highly relevant for HIV-1 Env immunogen design.

345 V1V2 Neutralizing Epitopes Are Conserved Within Divergent Groups of HIV-1

Marion Morgand[1]; Mélanie Bouvin-Pley[1]; Craig S Pace[2]; David Ho[2]; Pascal Poignard[3]; Marie Pancera[4]; Jean-Christophe Plantier[5]; Francois Simon[6]; Martine Braibant[1]; Francis Barin[7]

[1]Université de Tours, Inserm U966, Tours, France; [2]Aaron Diamond AIDS Research Center, The Rockefeller University, New York, NY, US; [3]Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, CA, US; [4]Vaccine Research Center, NIAID, NIH, Bethesda, WA, US; [5]Université de Rouen, CHU Charles Nicolle, Rouen, France; [6]Laboratoire de Virologie, Hôpital St Louis, Paris, France; [7]Université de Tours, Inserm U966, Laboratoire de Bactériologie-Virologie, CNR du VIH, CHU Bretonneau, Tours, France

Background: HIV-1 has been classified into 4 groups: M, N, O and P. These last years, highly potent broadly neutralizing monoclonal antibodies (bNabs) have been obtained from individuals infected by HIV-1 group M variants. The aim of this study was to analyze the cross-group neutralization potency of these bNabs using a large panel of non-M primary isolates (PI).

Methods: The sensitivity to neutralization of 16 non-M HIV-1 PIs (12 O, 2 N, 1 P, 1 M/O recombinant) was analyzed in a neutralization assay using TZM-bl cells. Twenty two HuMoNabs were used. VRC01, VRC03, 3BNC117 and five clonal variants of NIH45-46^{G54W} target the CD4 binding site (CD4bs). PG9, PG16, PGT145 and PG9-PG16-RH target the N160 glycan-V1V2 site. PGT121, PGT128 and 10-1074 target the N332 glycan-V3 site. 2F5, 4E10 and 10E8 target the MPER of gp41. 8ANC195 target a complex epitope spanning both Env subunits. Two bispecific antibodies that combine the inhibitory activity of an anti-CD4 with that of PG9 or PG16 (BibNabs) were included in the study (PG9-iMab and PG16-iMab).

Results: Cross-group neutralization was observed only with the bNabs targeting the N160 glycan-V1V2 site. Four group O PIs, one group N PI and the group P were neutralized by PG9 and or PG16 at low concentrations (0.04-0.9.39 μg/mL). None of the non-M PIs was neutralized by the bNabs targeting other regions at the highest concentration tested (10 μg/mL), except 10E8 that neutralized weakly two group O PIs (3.35-3.69 μg/mL). The BibNabs neutralized very efficiently all the non-M PIs with IC50 below 1 μg/mL, except two group O strains. The high potency of the BibNabs was mediated by the gp120-binding activity of PG9 and PG16 scFVs.

Conclusions: The N160 glycan-V1V2 site is the most conserved neutralizing site within the four groups of HIV-1. It makes it a potentially interesting target for development of HIV vaccine immunogens. The corresponding bNabs could be useful for immunotherapeutic strategies in patients infected by non-M variants.

346 Improving Neutralization Potency and Breadth by Combining Broadly Reactive HIV-1 Antibodies Targeting Major Neutralization Epitopes

Rui Kong[1]; Mark Louder[1]; Kshitij Wagh[2]; Robert Bailer[1]; Kelli Greene[3]; Hongmei Gao[3]; Michel Nussenzweig[4]; Bette Korber[2]; David Montefiori[3]; John Mascola[1]

[1]Vaccine Research Center, NIAID, NIH, Bethesda, MD, US; [2]Los Alamos National Laboratory, Los Alamos, NM, US; [3]Duke University Medical Center, Durham, NC, US; [4]The Rockefeller University, New York, NY, US

Background: The isolation of broadly neutralizing HIV-1 monoclonal antibodies (mAb) to distinct epitopes on the viral envelope glycoprotein (Env) provides the potential to use combinations of mAbs for prevention and treatment of HIV-1 infection. The potency and breadth of mAb combinations have not been well characterized.

Methods: Two sets of combiantions were tested for neutralization breadth and potency on 125 viruses in TZM-bl assay. Set I includes VRC07 (CD4bs), PG9 (V1V2-glycan), PGT128 (V3-glycan) and 10E8 (MPER). Set II substituted VRC07 and PGT128 with 3BNC117 and 10-1074. In each set, 6 double, 4 triple and 1 quadruple mAb mixtures were made by combining mAbs at equal concentration. To study the interaction of mAbs, the experimental IC50 titers were compared to the titers predicted based on additive model.

Results: All combinations showed substantially improved neutralization breadth and potency compared to the corresponding single mAbs. At an IC_{50} cutoff of 1 μg/ml, VRC07 neutralized 83% of viruses, representing the best coverage by a single mAb, while double combinations neutralized 89-98%, and all triple and quadruple combinations neutralized 98-100%. IC50 and IC80 heat maps showed that a positive antibody in the mix enabled neutralization of strains that were resistant to the negative antibody in the mix, suggesting that the complementary neutralization profiles of the individual mAbs contributed to the improved breadth. When the experimental IC50 titers were compared to IC50 predicted based on additive model, an overall less than two fold differences were observed for all combiantions, suggesting no substantial synergy or antagonism. In 15 out of 22 combinations, including all double and triple combinations with CD4bs, V1V2-glycan and MPER mAbs, small but statistically significat increases were observed in experimetnal titers when compared to the additive prediction.

Conclusions: All 22 double, triple and quadruple combiantions containing mAbs targeting CD4bs, V1V2 glycan, V3 glycan and MPER epitpes showed substaintially improved neutralization breadth and potency. Overall the improvement was closely predicted by additive effect model and explained by complementary neutralization profiles of single mAbs. Subtle but consistent favorable interactions were observed in some mAb combinations.

347 Improved Antibody Cross-Neutralizing Activity in HIV-1 Dual-Infected LTNP Patients

Maria Pernas[1]; Concepción Casado[1]; Victor Sanchez-Merino[2]; Alberto Sanchez-Merino[2]; Isabel Olivares[1]; eloisa Yuste[2]; Cecilio Lopez-Galíndez[1]

[1]Instituto de Salud Carlos III, Majadahonda, Spain; [2]Institut d'Investigacions Biomediquès, Barcelona, Spain

Background: HIV-1 infected individuals, classified as long-term non-progressors (LTNP), remain healthy for many years in absence of antiretroviral therapy, with stable CD4+ T lymphocyte counts and low levels of viral replication. Neutralization studies in sera from LTNPs with undetectable viremia, showed little neutralizing activity (Nab) because of a reduced antigenic stimulation of B cells. A broad NAb response has been associated with prolonged high-levels of antigenic stimulation, in terms of high viral load and viral diversity. In fact, patients infected with two different HIV-1 viruses showed enhanced heterologous NAb response. However, little is known about the neutralizing response in LTNP patients with dual infection (DI) .

Methods: Four DI versus 6 single-infected LTNP patients were compared in their Nab response. Both groups were matched according to years after HIV-1 diagnosis, viral loads and T CD4+ cell counts. NAb response in samples from DI versus single-infected patients, were tested in two samples. A fixed 1/200 serum dilution was tested against a previously described mini-panel of six recombinant viruses from 5 different subtypes and tropisms; Nab breadth, expressed as number of subtypes crossed, was analyzed. To investigate if broader Nab response was related to the viral diversity generated by the DI, diversity in the viral quasispecies was measured by calculating the Shannon Entropy.

Results: LTNP DI patients showed a Nab response (median of 3.0 ± 0.8) significantly ($p = 0.0018$) broader than single-infected patients (median of 1.1 ± 1.1). Association between the number of subtypes crossed and viral diversity (Shannon entropy) showed a high positive correlation ($p = 0.0022$, $r^2 = 0.071$). The median Shannon entropy value of the viral population was statistically ($p = 0.0011$) higher in DI (0.0775) than in single-infected (0.0150) patients, suggesting that the higher viral diversity due to DI was associated with a broader NAb response.

Conclusions: This study analyzed for the first time the neutralization breadth in LTNP patients dually-infected by HIV-1. The higher diversity within the quasispecies generated by HIV-1 DI has contributed to the improvement of neutralization breadth in LTNP patients. These results could be very useful for HIV research and vaccine strategies.

348 Characterization of CD4 Independent HIV-1 Envelope as Potential Immunogens

Lifei Yang[1]; Bradley Cleveland[1]; Andrea P. Jordan[2]; Patricia Polacino[1]; James A. Hoxie[2]; Shiu-Lok Hu[1]

[1]University of Washington, Seattle, WA, US; [2]University of Pennsylvania, Philadelphia, PA, US

Background: We reported earlier that removal of a highly conserved N-linked glycan N197 (N7) on the primary HIV-1 isolate 89.6 improved the immunogenicity of the envelope (Env) protein. Deletion of this glycan made the 89.6 Env more sensitive to CD4-binding site-specificantibodies (Abs) and less dependent on the CD4 receptor to initiate infection. However, it is not clear if the improvement in immunogenicity of 89.6 Env is related to the N7 glycan site mutation per se or the acquisition of a partial CD4i phenotype.

Methods: Here, we generated fully CD4i viruses derived from the WT and the N7 mutant of SHIV 89.6 and isolated Env clones that are replication competent in CD4-negative cells. CD4-independece was confirmed by evaluation of cloned Envs in cell fusion assay and on infectious viruses when cloned back into SHIV backbone.

Then we generated recombinant vaccinia viruses expressing CD4i 89.6WT (i89.6WT) and N7 (i89.6N7) mutant Envs. Antigenicity of these Envs on cell surface was analyzed using flow cytometry. Neutralization sensitivity of CD4i SHIV viruses was tested on TZM-bl cells. Biological function of these CD4i 89.6 Envs was tested by cell fusion assay.

Results: We isolated two i89.6 WT Env clones (A2 and B1) and one i89.6N7 Env clone (D4t), which were derived, respectively, from WT and N7 versions of SHIV 89.6. i89.6 N7-D4t Env maintains an intact CD4 binding site (bs), but CD4bs of i89.6-A2 and -B1 Envs are mutated. Cytoplasmic tails of all three Envs are truncated. In contrast to parental 89.6 WT and N7 Envs, i89.6 WT and N7 Envs can medicate cell-cell fusion in CD4-negative CCR5- and/or CXCR4-expressing cells. Only SHIV i89.6 WT and N7 viruses replicate in those CD4-negative cells.

Recombinant vaccinia viruses expressing i89.6 WT and N7 were generated. Full length i89.6WT and N7 Envs can be expressed, glycosylated and processed into gp120 and gp41. i89.6WT and N7 Envs expressed by vaccinia virus vectors mediate cell fusion and exhibit antigenic properties expected of native Env trimers. They preserve epitopes of most broadly neutralizing Abs tested, but they also show altered antigenicity compared to parental Envs.

Conclusions: Acquisition of the CD4i phenotype is accompanied by changes in the receptor/coreceptor binding properties of the Env and its antigenicity. How these changes may impact the immunogenicity of Env is being examined.

349 Phenotypic Neutralization Sieve Analysis of an SIV Nonhuman Primate Vaccine Challenge Study

Fang-Hua Lee[1]; Brandon F. Keele[3]; Robert Doms[1]; George M. Shaw[1]; Mario Roederer[2]; **Katharine J. Bar**[1]
[1]University of Pennsylvania, Philadelphia, PA, US; [2]Vaccine Research Center, NIAID, NIH, Bethesda, MD, US; [3]National Cancer Institute, Frederick, MD, US

Background: We previously characterized the neutralization sensitivity of the nonhuman primate (NHP) challenge stock SIVsmE660 and found the isolate was generally highly neutralization sensitive with a minor population of resistant variants (Lopker *et al*., J Virol 2013). We hypothesized that incomplete vaccine-mediated protection may result from protection against only the neutralization sensitive fraction of SIVsmE660. Subsequently, a large NHP vaccine study demonstrated incomplete protection from SIVsmE660 challenge and identified genotypic signatures associated with neutralization resistance (Roederer *et al*., Nature 2014). Here, we perform a phenotypic neutralization sieve analysis of the breakthrough TF viruses of this NHP vaccine study.

Methods: TF Env clones were derived by single genome sequencing of peak plasma vRNA from the breakthrough infections in heterologous Env-immunized animals (n=18 TF Envs) and controls (n=35 TF Envs). Neutralization sensitivity was assessed in a TZM-bl assay with SIV-infected macaque plasmas and a panel of 10 monoclonal antibodies (mAb) targeting V1, V2, V3, V4, CD4bs and CD4i epitopes.

Results: The breakthrough TF Envs from immunized animals were significantly more neutralization resistant to immune plasma and mAbs targeting diverse gp120 epitopes than those from control animals. The maximum reductions in infectivity from plasma were 74.6% in control Envs, and 40.3% in vaccine Envs ($p<0.0001$, Mann-Whitney). The majority of vaccine TF Envs (13/18, 72%) were highly neutralization resistant (IC50<1:10), compared with the fraction comprising the control TF Envs (6/35, 17%, $p=0.0002$) and the SIVsmE660 isolate (10%, $p=0.0002$). The genotypic signatures of resistance identified in the Roederer study were highly predictive of phenotypic neutralization sensitivity.

Conclusions: We demonstrate a phenotypic neutralization sieve effect in a large NHP vaccine challenge study with substantial enrichment for neutralization resistant viruses in the breakthrough infections of vaccinated animals. These findings support our hypothesis that incomplete vaccine-mediated protection results from selection against the highly neutralization sensitive component of the SIVsmE660 isolate. Further, we corroborate the genetic signatures of SIVsmE660 neutralization sensitivity predicted in the parent study. Together, these findings demonstrate proof-of-concept that phenotypic neutralization sieve analyses may be useful in assessment of vaccine trial outcomes and correlates analysis.

350 AvFc, a Novel Fc Fusion Protein Targeting Env High-Mannose Glycans

Nobuyuki Matoba; Adam Husk; J. Calvin Kouokam; Krystal Hamorsky; Tiffany Grooms-Williams; Garima Mahajan
University of Louisville James Graham Brown Cancer Center, Owensboro, KY, US

Background: AvFc is a recombinant fusion protein consisting of the high-mannose glycan-binding lectin Avaren and the Fc region of a human IgG1. We have previously shown that AvFc exhibits sub to low-nanomolar neutralization activity against a broad spectrum of HIV-1 and -2 primary strains and HCV genotypes. The objective of this study is to investigate the feasibility of AvFc for use in HIV prevention and/or treatment.

Methods: Combinations of AvFc and other HIV inhibitors were evaluated in HIV-1 neutralization assays. Surface plasmon resonance (SPR) and flow cytometry were used to analyze binding characteristics of the Fc region of AvFc. FcγRIIIa receptor activation was analyzed using an Env-expressing and a Jurkat reporter cell lines. Flow cytometry, multiplex cytokine assay and quantitative PCR were used to test inflammatory potential in human peripheral blood mononuclear cells (PBMC). Rabbit and mouse vaginal irritation models were used to assess vaginal toxicity, while mice and rats were used to examine immunogenicity and systemic toxicity, respectively.

Results: AvFc exhibited synergism with Tenofovir, Maraviroc and VRC01 (combination index << 0.8, CalcuSyn software) against multiple HIV-1 strains. AvFc bound to FcγRI, FcγRIIIa, FcRn and C1q with affinities similar to those of human IgG_1. Furthermore, the FcγRIIIa activation assay indicated that AvFc is capable of inducing antibody-dependent cell-mediated cytotoxicity. Unlike concanavalin A, AvFc had little cytotoxicity, mitogenicity or proinflammatory activity in human PBMC up to 100 μg/ml, which is >1,000 times median anti-HIV IC_{50}. In addition, AvFc did not induce any discernible toxic or inflammatory effects in both vaginal models. Repeated injection of Avaren with an adjuvant did not elicit any significant anti-Avaren IgG response in mice, which is indicative of low immunogenicity; being a small protein (12.5 kDa) with three tandem sequence repeats, Avaren may contain few, if any, T cell epitopes. A single intravenous infusion of 4 mg/kg AvFc in rats did not show any sign of toxicity; no weight loss or behavioral change was observed. Additionally, the complete blood count and serum chemistry of terminal blood samples appeared to be normal.

Conclusions: Our data suggested that AvFc is a unique anti-HIV agent exhibiting broad HIV-neutralizing activity and Fc-mediated functions, and appears to be safe for mucosal and/or systemic administration.

351 DARPins as Entry Inhibitor Alternative to HIV-1 Broadly Neutralizing Antibodies

Emanuel Stiegeler; Nikolas Friedrich; Thomas Reinberg; Mylène Morin; Yufan Wu; Jonas V. Schaefer; Peter Rusert; John Robinson; Andreas Plückthun; Alexandra Trkola
University of Zurich, Zurich, Switzerland

Background: Development of drugs that share the properties of broadly neutralizing antibodies (BNAbs) is highly desirable. Here we utilize the Designed Ankyrin Repeat Protein (DARPin) technology to generate HIV-1 inhibitors with broad neutralization activity directed against the V3 loop. DARPins, small synthetic binding proteins with high target affinities and specificities, have interesting properties as anti-HIV inhibitors in particular as they can recognize their target in a structure dependent manner (Mann A, J Virol 2013).

Methods: V3 specific DARPins were selected from 1st and 2nd generation high diversity molecular DARPin libraries, the latter featuring additional randomized positions in the binding surface and a higher overall stability of the DARPin scaffold. Recombinant gp120 and a structurally arrested V3 epitope mimetic were used as panning targets during

ribosome display selection rounds. The resulting sub-libraries were screened by binding ELISA and pseudovirus neutralization assay. Epitopes were mapped by alanine-scan and characterized by competition ELISA.

Results: Focusing selection of DARPins on the V3 loop using a structurally arrested V3 mimetic proved to be successful. The selected DARPins varied in their binding preference for specific V3 structures and most importantly, showed different degrees of neutralization breadth. As the panning targets were of subtype B origin, the neutralization activity of DARPins was mostly restricted to this subtype. This was improved using the 2nd generation DARPin library, from which we selected a novel type of V3 DARPin with broad neutralization capacity. DARPin 13.2 G10 neutralizes 62.5% of pseudoviruses out of 32 viruses from 5 different clades.

Conclusions: The structurally arrested V3 mimetic proved to be a valuable tool to focus the selection of DARPin clones to V3 and to derive a broadly active entry inhibitor. This result opens novel opportunities for selecting HIV-1 inhibitory DARPins specific for different epitopes.

WEDNESDAY, FEBRUARY 25, 2015

Session P-E3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

New Approaches to Immunostimulation

352 Use of Pre-ART-Adjusted Endpoints in the Analysis of an HIV Therapeutic Vaccine Trial

Yunda Huang[1]; Lily Zhang[1]; Darren Jolliffe[3]; Arnt-Ove Hovden[4]; Mats Okvist[4]; Pantaleo Giuseppe[2]; Maja A. Sommerfelt[4]

[1]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [2]Lausanne University Hospital, Lausanne, Switzerland; [3]S-cubed Biometrics Ltd, Oxfordshire, United Kingdom; [4]Bionor Pharma ASA, Oslo, Norway

Background: In one of the largest randomized, double-blind, placebo-controlled phase 2 therapeutic HIV vaccine clinical trials, Vacc-4x was found safe, well-tolerated and immunogenic. While on combination antiretroviral therapy (cART), 135 HIV-infected participants (vaccine: placebo = 92: 43) were randomized and received 4 weekly immunizations followed by booster immunizations at weeks 16 and 18. At week 28, cART was interrupted for up to 24 weeks. Based on the primary analyses, Vacc-4x did not significantly reduce the proportion of participants resuming cART or change in CD4 counts during the cART interruption. We assessed the vaccine effect based on additional exploratory endpoints.

Methods: All analyses included per-protocol (PP) participants who received the full immunization and underwent cART interruption. Linear regression models were used to identify predictors of outcomes measured after cART interruption, and to estimate the vaccine effect adjusted for potential baseline confounding factors. We assessed vaccine effect based on four novel preART-adjusted clinical endpoints: fold changes in CD4 counts at week 40 or in the geometric mean of CD4 counts at weeks 48 and 52 over preART CD4 counts, and fold changes in viral load (VL) at week 40 or in the geometric mean of VL at weeks 48 and 52 over preART VL. We used a multiple imputation approach to account for missing CD4 counts or VL due to cART resumption or dropout.

Results: PreART CD4 counts and VL were significant predictors of levels after cART interruption. A significant vaccine effect was observed in the analysis of all four preART-adjusted endpoints. Compared to the placebo recipients, the vaccine recipients had a higher fold change in week 40 CD4 counts (vaccine vs. placebo mean fold-change difference = 0.08; 95% CI 0.02, 0.15; p=0.02), a higher fold change in weeks 48/52 CD4 counts (0.07; 95% CI 0.01, 0.13; p=0.03), a lower fold change in week 40 VL (-0.46; 95% CI -0.88 to -0.04; p=0.03), and a lower fold change in weeks 48/52 VL (-0.44; 95% CI -0.86, -0.02; p=0.04).

Conclusions: These exploratory analyses consistently suggested that Vacc-4x provided improved effect on preART-adjusted clinical endpoints for CD4 counts and VL over participants' preART conditions. Future HIV therapeutic vaccine studies may adopt similar endpoints of fold changes over preART values to account for participants' heterogeneity and to increase the statistical power of vaccine effect evaluations.

353 Decreased HIV-Specific T-Regulatory Responses Mark Effective Vaccine-Induced Immunity

Vedran Brezar[1]; Nicolas Ruffin[1]; Laura Richert[2]; Mathieu Surenaud[1]; Christine Lacabaratz[1]; Karolina Palucka[3]; Rodolphe Thiebaut[2]; Jacques Banchereau[1]; Yves Lévy[1]; Nabila Seddiki[1]

[1]Inserm U955 (Eq16)-UPEC-VRI, Créteil, France; [2]Univ Bordeaux-ISPED-Inserm U897-VRI, Bordeaux, France; [3]Ralph M. Steinman Center for Cancer Vaccines–Baylor Institute for Immunology Research, Dallas, TX, US

Background: The role of regulatory T cells (Tregs) in vaccination has been poorly investigated. We have reported that vaccination with *ex vivo*-generated dendritic-cells (DC) loaded with HIV-lipopeptides (LIPO-5-DC vaccine) in HIV-infected patients was well tolerated and highly immunogenic. However, patients responded differently to vaccination. Here we hypothesized that the presence and/or induction of HIV-specific Tregs might explain this observation.

Methods: Fourteen HIV-1 infected individuals under effective antiretroviral therapy have been included in this study. Patients received LIPO-5-DC vaccine every 4 weeks during 16 weeks period. Blood was drawn prior (week -4) and after (week 16) vaccination. This was followed by analytical treatment interruption (ATI) at week 24 to measure the magnitude of viral rebound. To assess the antigen-specific effectors (Teffs) and Tregs responses, a novel assay was used in which coexpression of CD25 and CD134 reveals these cells after stimulation *in vitro*. CD39 and FoxP3 markers were used to delineate antigen-specific Tregs and distinguish them from effector specific- responses.

Results: Median LIPO-5-specific $CD25^+CD134^+$ polyfunctional T cells increased from 0.1% (IQR 0-0.3) before vaccination (week -4) to 2.1% (IQR 1.1-3.9) at week 16 following 4 immunizations (P=0.001) and were inversely correlated with viral replication following ATI (r=-0.71, p=0.006). The frequency of LIPO-5-specific Tregs prior to vaccination was elevated, accounting for a median 69.3% (IQR 55.8-75.2) of LIPO-5-specific response. After vaccination, the frequency of HIV-specific Tregs decreased (from 69.3 at week -4 to 31.7% at week 16) and inversely correlated with the HIV-specific IFNγ-producing cells (r=-0.64, P=0.002). These Tregs are highly suppressive as their depletion prior to stimulation led to a further increase in IFNγ responses. Vaccinees who displayed lower levels of LIPO-5-specific $CD4^+CD134^+CD25^+CD39^+FoxP3^+$ Tregs responded better to the vaccine as indicated by a negative correlation between LIPO-5-specific Tregs and post-vaccination immune score.

Conclusions: We show that DC-vaccine skewed the HIV-specific response from regulatory to effector phenotype. Patients with lower magnitude of viral replication following ATI presented lower levels of HIV-specific Tregs. This underlies the role these cells play in HIV-infection and the necessity to take them into account for future vaccine trials.

354 Viral Reservoir Dynamics After Therapeutic Vaccination and cART Interruption

Cristina Andres[1]; Carmen Alvarez-Fernandez[1]; Nuria Climent[1]; Teresa Gallart[1]; Montserrat Plana[1]; Agathe Leon[1]; Nicolas Chomont[2]; Jose M. Gatell[1]; **Felipe Garcia**[1]; Sonsoles Sanchez-Palomino[1]

[1]Hospital Clinic, Barcelona, Spain; [2]Vaccine and Gene Therapy Institute, Port St Lucie, FL, US

Background: We reported a decrease viral set-point of 1.2 log10 associated with an increase in HIV-1–specific T cell responses in HIV infected individuals receiving autologous myeloid derived dendritic cells (MDDC) pulsed with autologous heat-inactivated whole HIV. Here, we assessed changes in viral reservoirs during vaccinations and the dynamics of viral reservoir replenishment during cART interruption after immunizations.

Methods: 36 patients on cART were randomized to 3 immunizations with MDDC pulsed with HIV-1 (n=24) (cases) or with non-pulsed MDDCs (n=12) (controls). Virus for pulsing was isolated 56 weeks before the first immunization during a first cART interruption (STOP 1). Thereafter, cART was reinitiated and after 48 weeks 3 immunizations were performed and cART was interrupted again (STOP2). We measured total and integrated HIV-1 DNA in isolated CD4 T cells before any cART, before STOP1 (preSTOP1), before and after vaccination (VAC1 and VAC2) and at week 12 after second interruption of cART (STOP2). Data are expressed as mean log_{10} copies/10^6 CD4 T cells.

Results: As expected, we observed a drop in total and integrated DNA after the 3 years on cART from the precART period (3.8 and 2.6, respectively) to the time point before STOP1 (3.0 and 1.9, respectively) in the 36 patients ($p<0.0001$ for both comparisons). Three months of cART interruption at STOP1 followed by 9 months of cART did not modify total and integrated DNA in these 36 subjects (VAC1 values: 3.0 and 1.9) ($p=0.41$ and $p=0.62$ as compared with preSTOP1). Vaccination (VAC1 to VAC2 period) did not influence DNA levels in vaccinated subjects (n=24) [total DNA from 2.9 (VAC1) to 2.9 (VAC2), $p=0.86$ and integrated DNA 1.9 (VAC1) to 1.8 (VAC2), $p=0.47$]. After cART interruption post-vaccination (STOP2), while total DNA significantly increased in both vaccinees (n=24) and controls (n=12) (2.9 to 3.3, $p=0.0004$ and 3.2 to 3.7, $p=0.009$, respectively), integrated DNA did not change in vaccinees (1.8 to 1.9, $p=0.22$) and increased in controls (1.8 to 2.1, $p=0.05$). Moreover, these changes in integrated DNA after STOP2 were inversely correlated with changes in HIV specific T cell responses in cases ($r= -0.54$, $p=0.03$), while no correlation was observed in controls ($r= -0.16$, $p=0.74$).

Conclusions: No change in total and integrated DNA was observed after 3 months of cART interruption followed by 9 months of cART. HIV-1 specific immune responses elicited by a therapeutic DC vaccine prevented an increase in integrated DNA after cART interruption.

355 HIV-1 Envelope Epitope Recognition Is Influenced by Immunoglobulin D_H Gene Segment Repertoire

Yuge Wang[2]; Aaron Sanchez-Silva[2]; Barton Haynes[1]; Harry Schroeder[2]

[1]Duke University, Durham, NC, US; [2]University of Alabama at Birmingham, Birmingham, AL, US; [3]University of Alabama at Birmingham, Birmingham, AL, US

Background: HIV-1-specific broadly neutralizing antibodies (BnAbs), such as the membrane proximal external region (MPER) antibodies 2F5 and 4E10, contain long H chain complementarity determining region 3 (CDR-H3) which is encoded by D_H gene segment, that lacks tyrosine and includes patches of hydrophobic and charged amino acids. However, B cells bearing Igs with charged or hydrophobic CDR-H3s are normally culled from mature B cell subsets. Thus, elucidation of mechanisms that underlie the difficulty in generating HIV-1 can be seen as a part of fundamental need to better understand how to distinguish self and non-self receptors that can neutralize pathogenic antigens without self-inflicting dame to the host.

Methods: Mice-BALB/c mice cohort limited to the use of single D_H gene segments were generated. ΔD-DFL is a human-like repertoire control. ΔD-DμFS promotes the use of hydrophobic amino acid CDR-H3. The ΔD-iD is charged amino acid enriched CDR-H3. **Immunization**-each strain of 10 mice was immunized with HIV-1 JR-FL gp140 protein. **Epitope Identification**-Two group of mice (No. 4 & 5) of each strain were selected (prior to immunization, and after the 2nd and 4th immunizations) for PEPperPRINT Chip to detect their epitopes on HIV-1 JR-FL gp140. **Serum Assay**-Binding ability was examined by HIV-1 envelope protein ELISA. Blocking activity was examined by competitive ELISA with soluble CD4 (sCD4) and 2F5, 2G12 antibodies.

Results: 1. We obtained evidence of strong and clear polyclonal responses to immunization with JR-FL gp140. As a general rule, the heterogeneity of the anti-JR-FL gp140 response varied by D_H genotype with ΔD-DFL>Wild Type (WT)>>ΔD-DμFS, ΔD-iD. Conversely, the intensity of the response was greatest in the ΔD-iD.

2. Linear response showed by PEPperPRINT chip was not identified with the response to natural HIV-1 epitopes, however, the ΔD-iD favored charged epitopes that is inconsistent with our hypothesis.

3. Anti-JR-FL gp140 antibodies present in the sera of the D_H altered did not block HIV-1 envelope CD4, 2F5, 2G12 binding site. This suggests reduced affinity, stability or on rates, or increased off rates for Igs obtained from D_H altered mice.

Fig1. D_H Altered Mice Cohorts and Immunization

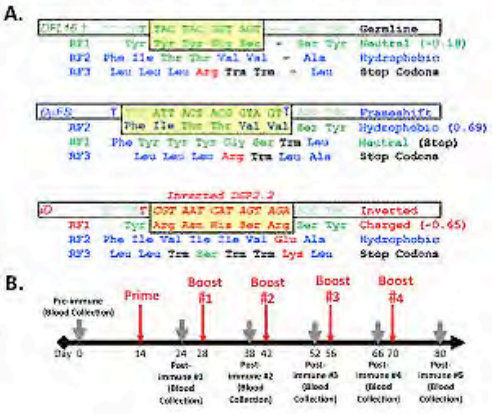


Fig3. Alteration of D_H Sequence Biases Anti-HIV-1 Linear Peptide Response Preference.

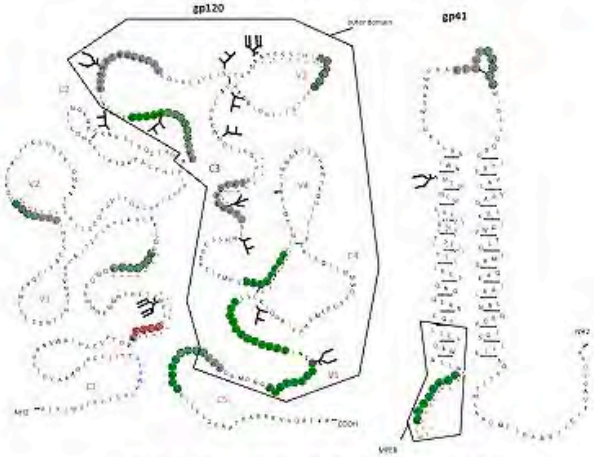


Fig2. Alteration of D_H Sequence Biases Anti-HIV-1 Gp160 Epitope Preference

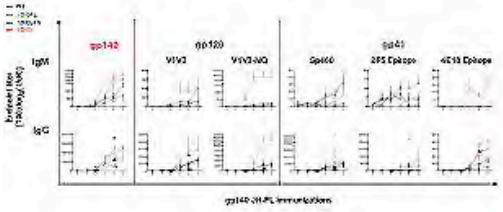
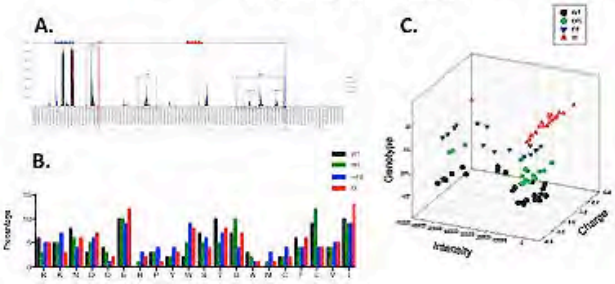


Fig4. D_H Altered Mice Shifts the Amino Acid Usage of Responding HIV-1 Epitopes



Conclusions: The pattern of epitope recognition and antigen binding in the response to HIV-1 JR-FL gp140, in part, is on D_H gene segment sequence. Restrictions imposed by natural selection of D_H sequence may underlie some of the difficulty that patients experience in HIV-1 neutralizing antibody.

356 Human Rhinovirus Displaying HIV-1 4E10 Epitope Elicits Broad Neutralization in hICAM-1 Tg Mice

Guohua Yi[1]; Xiongying Tu[2]; Preeti Bharaj[1]; Premlata Shankar[1]; Manjunath Swamy[1]

[1]Texas Tech University Health Sciences Center, El Paso, TX, US; [2]University of Minnesota, St Paul, MN, US

Background: Induction of bnAbs remains a critical goal towards developing a vaccine against HIV-1. We previously grafted 4E10 epitope of HIV-1 gp41 on the surface of human rhinovirus connected via linkers of varying lengths and sequences to construct combinatorial HRV display libraries. One chimeric HRV:HIV immunoselected from the libraries was able to elicit broad neutralization against 10 of 12 HIV-1 pseudoviruses in guinea pigs. However, guinea pigs do not get infected with HRV because they lack the viral receptor, human ICAM-1 and thus the antibody titers were rather modest. Since the recently developed hICAM-1 Tg mice support productive HRV infection, in this study we evaluated the efficacy of chimeric HRV:HIV vaccine in these mice.

Methods: hICAM Tg mice were intranasally immunized with three representative chimeric HRV:HIV viruses chosen from our previous study. The sera collected at different time points were tested for immunogenicity and HIV neutralization. ELISA was used to test the binding affinity against 4E10 peptide as well as HIV-1 gp140 trimer. The neutralizing ability against HIV-1 isolates was tested by single-round Tat-regulated luciferase assay in TZM-bl cells. Also, 11 HIV-1 internationally circulating isolates of diverse subtypes and coreceptor usages were used to test the breadth of neutralizing ability. HRV pre-immunized Tg mice were further immunized with chimeric HRV:HIV to test whether nasal administration can bypass HRV pre-immunity.

Results: The sera from the immunized mice showed good binding affinity with 4E10 peptide as well as with HIV-1 gp140 trimer. All three chimeric HRV:HIV elicited neutralizing antibody responses in hICAM-1 Tg mice against diverse isolates of HIV-1, with one eliciting anti-HIV antibodies capable of neutralizing 9 of the 11 internationally circulating HIV-1 isolates at IC50 level (from six subtypes and two co-receptor usages of HIV-1). Furthermore, intranasal administration of chimeric HRV:HIV could bypass the preexisting immunity to HRV to elicit anti-HIV response.

Conclusions: This work demonstrates that productive infection of HRV susceptible animals with chimeric HRV effectively elicits broadly neutralizing anti-HIV-1 antibodies. This strategy therefore appears to have potential for human vaccination.

357 WITHDRAWN

358 A Superagonist Antibody to Human Interleukin-21 Increases HIV-Specific T-Cell Function

Yew Ann Leong[1]; Yanfang Cui[1]; Zhian Chen[1]; Fiona Wightman[1]; Pellegrini Marc[2]; Jamie Rossjohn[1]; Sharon R. Lewin[3]; Alan Landay[4]; Charles Mackay[1]; Di Yu[1]

[1]Monash University/Alfred Hospital, Melbourne, Australia; [2]Walter and Eliza Hall Institution, Melbourne, Australia; [3]University of Melbourne, Melbourne, Australia; [4]Rush University Medical Center, Chicago, IL, US; [5]Monash University/Alfred Hospital, Melbourne, Australia

Background: Interleukin-21 (IL-21) is an immunostimulatory cytokine showing promising results in phase II clinical trials for cancer immunotherapy. IL-21 also enhances anti-viral immunity in HIV/SIV infections. It is a suitable candidate that can be targeted by the kick and kill strategy to boost immunity to eliminate HIV. This study focused on developing an agonistic monoclonal antibody (mAb) to human IL-21 (hIL-21) that enhances the anti-viral function of hIL-21.

Methods: A hIL-21-dependent Ba/F3 cell line proliferation assay was used to screen a library of anti-hIL-21 mAbs to identify agonistic clones. Binding of the agonist mAb to hIL-21 was characterized by Surface Plasmon Resonance (SPR) and crystallography. To test the anti-HIV function of the mAb, peripheral blood mononuclear cells (PBMCs; n=5) from HIV infected patients on antiretroviral therapy (ART>3 years, $CD4^+$ T-cell count>500/μL, viral load<50 copies/mL) were stimulated with MHC-I-restricted gag peptides in the presence of hIL-21 and the mAb. Cytotoxicity of natural killer (NK) and $CD8^+$ T cells were analyzed by measuring intracellular granzyme B and perforin expression by flow cytometry (FACS). The phamacokinetics and phamacodynamics of the mAb were studied in mice humanized with hIL-21 and the hIL-21 receptor (hIL-21R) and infected with lymphocytic choriomeningitis virus (LCMV). Bioavailability (BA) of hIL-21 with the mAb was measured by enzyme-linked immunosorbent assay. Agonistic effect of mAb was determined by quantifying virus-specific $CD8^+$ T-cell response by FACS and viral load by plaque assay.

Results: We identified a mAb SG1 that enhanced hIL-21's activity ≥10 folds in the Ba/F3 cell proliferation assay. It bound to hIL-21 with an affinity of 7.1E-11(K_D). Crystal structure and protein docking stimulation revealed that SG1 changed the conformation of hIL-21 to suit its binding to the receptor. In cultured PBMCs from HIV-infected patients, SG1 significantly increased the cytotoxicity of NK and $CD8^+$ T cells by 5-10 folds. In the chronic LCMV infection, SG1 increased the BA of hIL-21 >50 folds. An enhanced generation of functional virus-specific CD8+ T cells led to early resolution of the infection.

Conclusions: The high-affinity mAb SG1 has a unique function to enhance hIL-21's activity by changing its conformation and increasing the BA *in vivo*. Superagonist mAb SG1 promotes the anti-viral function of hIL-21 *in vitro* and *in vivo*. SG1 might be used in a kick and kill approach to eliminate HIV latency.

THURSDAY, FEBRUARY 26, 2015

Session P-E4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Cellular Immune Response to HIV

359 Evolution of HIV-Specific CD8+ T-Cell Responses in Hyperacute HIV Infection

Zaza M. Ndhlovu[1]; Nikoshia Mewalal[1]; Philomena Kamya[1]; Thandeka Nkosi[1]; Karyn Pretorius[1]; Nasreen Ismail[1]; Amber Moodley[2]; Krista Dong[2]; Thumbi Ndung'u[1]; Bruce Walker[2]

[1]University of KwaZulu-Natal, Durban, South Africa; [2]Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, US

Background: $CD8^+$ T cells suppress HIV replication, but the relationship to initial onset of plasma viremia has not been well defined since acute infections are rarely identified prior to peak viremia. Moreover, pre-infection samples are rarely available.

Methods: To address evolving viral and T cell dynamics from the onset of plasma viremia, hyperacute cases of HIV infection were identified by biweekly HIV RNA screening of plasma from high risk uninfected women in KwaZulu-Natal, South Africa, as part of a comprehensive HIV prevention program. Pre-infection and post infection blood samples were evaluated in 12 subjects identified with initial viral load as low as 140 RNA copies/ml plasma. Assays performed on fresh and/or cryopreserved cells included intracellular cytokine staining (Ki67, Bcl-2, CD38, HLA-DR, CD107a, IFN-g, TNF-a and IL-2) as well as IFN-g ELISPOT and class I tetramer staining.

Results: Onset of HIV viremia rapidly induced massive activation of CD8+ T cells from 0.27% (*IQR 0.87 to 0.88*) pre-infection to 52.7% (*IQR 41.8 to 67.4*) (*p<0.0001*), by day14 post onset of plasma viremia. In contrast, Influenza and CMV-specific CD8+ T cells were minimally activated, indicating that bystander activation was not occurring. HIV-specific responses were already detectable prior to peak viremia. Duration to highest frequency of activated T cells and the magnitude of the initial response both had a significant association with lower viral load set point (*time to peak activation, Spearman's r=0.7, p=0.02; magnitude at peak activation, Spearman's r=-0.7, p=0.02*). Stimulation with exogenously infected autologous CD4+ T cells revealed that at least 74% of the early proliferating CD8+ T cell response was HIV-specific with the capacity to degranulate and secrete cytokines. Acute phase HIV-specific CD8+ T cells were prone to apoptosis due to activation induced cell death but this resolved after viral load set point was achieved.

Conclusions: Our data provide strong evidence that the initial CD8+ T cell response to HIV is much larger than previously appreciated, but is highly proapoptotic and rapidly declines despite ongoing viremia. The rapidity and magnitude of the earliest response are key factors for successful control, as both inversely correlated with subsequent viral load set point. Overall, these studies suggest that, to facilitate long-term control, the initial CD8+ T cell response must be swift, of high magnitude and sustained.

360 Nonclassical Regulatory HIV-1–Specific CD8 T Cells in HIV-1 Disease Progression

Selena Vigano[2]; Chun Li[2]; Jordi J. Negron[2]; Bruce D. Walker[2]; Mathias Lichterfeld[1]; Xu G. Yu[2]

[1]*Massachusetts General Hospital, Boston, MA, US;* [2]*The Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, US*

Background: Regulatory T cells may influence HIV-1 disease progression by suppressing immune activation or inhibiting antiviral T cell immune responses. Recently, a distinct population of non-classical regulatory T cells expressing HLA-G was identified. However, the role of HLA-G-expressing T cells specific for HIV-1 is unknown.

Methods: 36 HIV-1-specific and 25 CMV/EBV-specific CD8 T cell responses were analyzed in 47 HIV-1 infected patients. 27 patients were chronic progressors with median HIV-1 viral loads of 50,300 copies/ml and median CD4 T cell counts of 456 cells/ul. 20 patients were controllers with viremia below 1000 copies/ml and CD4 T cell counts above 600 cells/ul. HLA-G expression on HIV-1 specific CD8 T cells was assessed by multimer staining and flow cytometry. Cytokine production of sorted HLA-G+ and non-regulatory CD8 T cells was assessed in 12 HIV-1 negative individuals following CD3/CD28 stimulation by Luminex.

Results: The frequency of HLA-G+ HIV-1 specific (*P*=0.0002), but not CMV- or EBV-specific (*P*=n.s) CD8 T cells, was increased in controllers when compared to chronic progressors. This increase was mostly driven by HLA-G+ CD8 T cells restricted by protective HLA class I alleles (*P*<0.004), while no difference between controllers and chronic progressors was observed when CD8 T cells restricted by non-protective alleles were analyzed. The proportion of HLA-G+ HIV-1-specific CD8 T cells was directly associated with CD4 T cell counts (*P*=0.0002, r=0.57) and inversely with viral loads (*P*<0.0001, r=-0.66), while total HIV-1-specific CD8 T cells were not. Of interest, HLA-G+ CD8 T cells produced higher amount of IL-10, IL-2, MIP-1α, MIP-1β and RANTES than HLA-G-negative CD8 T cells after anti-CD3/amti-CD28 stimulation.

Conclusions: These data indicate a potentially protective role of HIV-1-specific HLA-G+ regulatory CD8 T cells on HIV-1 disease progression. The production of MIP-1 α, MIP-1 β and RANTES may be pivotal in controlling HIV-1 replication. Further investigations of functional properties of these non-classical regulatory CD8 T cells are necessary in order to better elucidate their role in HIV immunopathogenesis.

361 Nef Plays a Role in the Resistance of SIV-Infected Macrophages to CD8+ T-Cell Suppression

Jennifer N. Rainho; Mauricio A. Martins; Francesc Cunyat; David I. Watkins; Mario Stevenson

University of Miami, Miami, FL, US

Background: SIV-specific CD8+ T cells kill SIV-infected CD4+ T cells in a MHC Class I (MHC-I) dependent manner. However, they are less efficient at killing SIV-infected macrophages. Since Nef has been shown to down regulate MHC-I molecules and enhance CTL evasion, we examined if Nef played a role in protecting SIV-infected macrophages from killing by freshly sorted SIV-specific CD8+ T cells.

Methods: The viral suppression assay (VSA) involves the co-culture of primary SIV-infected CD4+ T lymphocytes or monocyte-derived macrophages (target cells), with enriched, primary unstimulated SIV-specific CD8+ T cells (effector cells) for 24 hrs. Suppression of viral replication was determined by an antigen capture assay for Gag p27 in culture supernatants. Elimination of infected target cells was assessed by flow cytometric quantification of Gag p27+ target cells in the presence and absence of effectors. To explore the role of Nef in CD8+ T cell evasion, target cells were infected with wild type SIVmac239 (239wt-*nef*), *nef*-deleted SIVmac239 (239Δ*nef*), and a Nef point mutant (Y223F–*nef*) shown previously to inactivate the ability of Nef to down regulate MHC-I. Our controls included SIV-infected target cells in the absence of effectors and SIV-infected target cells isolated from animals with mismatched MHC-I alleles.

Results: Freshly sorted SIV-specific CD8+ T cells eliminated SIV-infected CD4+ T cells, but not SIV-infected macrophages (p=<0.0001). Suppression of viral replication was also observed in cultures of CD4+ T cells, but not in SIV-infected macrophage cultures (p=0.0031.) Interestingly, we observed enhanced killing of macrophages infected with 239Δ*nef* (p= 0.0276) compared to macrophages infected with wild type virus. The sensitivity of 239Δ*nef* -infected macrophages to CD8+ T-cell-mediated suppression was not fully recapitulated in Y223F–*nef*-infected macrophages despite the fact that the point mutant was almost as effective as Nef-deleted SIVmac239 in disrupting MHC-I down regulation.

Conclusions: SIV-infected macrophages evade CD8+ T cell suppression. Nef may be involved in the resistance of infected macrophages to CD8+ T-cell-mediated suppression. However, this protective effect cannot be fully explained by Nef's ability to down regulate MHC-I. This study has implications for viral persistence and suggests that macrophages may afford primate lentiviruses some degree of protection from immune surveillance.

362 Defining Efficacious HIV-Specific CTL Responses Using Saporin-Conjugated Tetramers

Ellen M. Leitman[1]; Stuart Sims[2]; Rebecca P. Payne[1]; Fabian Chen[3]; Lynn Riddell[4]; Soren Buus[5]; Steven Deeks[6]; Bruce Walker[7]; Philippa C. Matthews[1]; Philip J. Goulder[1]

[1]*University of Oxford, Oxford, United Kingdom;* [2]*ETH Zurich, Basel, Switzerland;* [3]*Royal Berkshire Hospital, Reading, United Kingdom;* [4]*Northamptonshire Healthcare NHS Trust, Northampton, United Kingdom;* [5]*University of Copenhagen, Copenhagen, Denmark;* [6]*University of California San Francisco, San Francisco, CA, US;* [7]*Ragon Institute of MGH, MIT and Harvard, Charlestown, MA, US*

Background: *In vitro* killing of HIV-infected cells by cytotoxic T lymphocytes (CTL) is a surrogate marker of CTL antiviral efficacy. Tetrameric peptide-MHC complexes (tetramers) enable identification of antigen-specific CD8+ T cells in a mixed population. Due to their rapid internalization by cognate T cells, tetramers are an effective delivery vehicle of any coupled moiety to target specific CTL. Novel tetramers conjugated to saporin (SAP), a potent toxin causing cell death through ribosome-inactivation, have been used *in vivo* to deplete murine diabetogenic T cells, but no human reports exploiting this technology exist to date. Here, we used toxic tetramers to rapidly eliminate or 'zap' human CTL of different specificities in order to compare their anti-HIV potency.

Methods: PBMC were treated with HLA-matched SAP-coupled tetramers (tet-SAP) or a control (HLA-matched tet-PE, HLA-mismatched tet-SAP, free SAP) and cell loss was quantified by flow cytometry. In inhibition assays, CD8+ T cells were expanded, treated with tet-SAP or a control and added as effectors to HLA-matched target cells infected with NL4-3-GFP, used as a marker to measure viral inhibition.

Results: We show that HLA-matched tet-SAP but not HLA-mismatched tet-SAP or free SAP selectively binds to the surface of antigen-specific CD8+ T cells and is then rapidly internalized by the cognate cells alike a conventional tet-PE of the same specificity. We further show that, by as little as 48h post-tet-SAP treatment, up to 97% of tetramer-specific cells are eliminated from the diverse CTL population (Fig 1A). This elimination is highly targeted pertaining exclusively to the desired specificity. Finally, we compare the abilities

of zapped, untreated or control-treated CTL to inhibit viral replication, using CD8+ T cells from an HLA-B*27:05+ controller with the dominant B*27:05-Gag-KK10 response. We observe that untreated bulk and control-treated CD8+ T cells effectively inhibit viral replication, but zapped CTL lacking KK10-specific cells lose this suppressive capacity (Fig 1B).

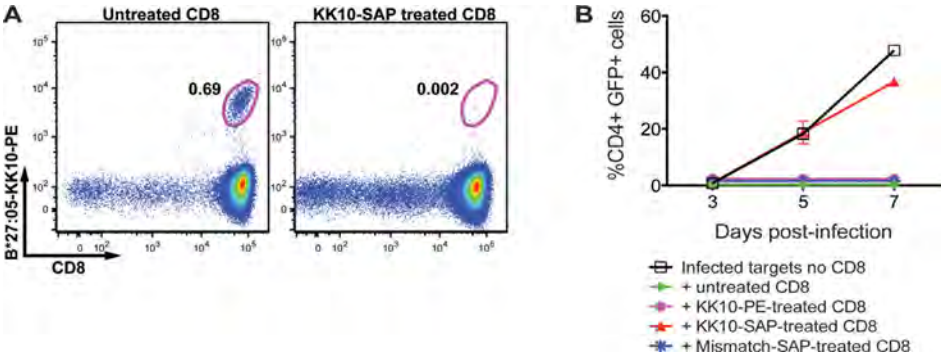


Figure: (A) Representative FACS plots showing HLA-B*27:05-KK10+ CD8+ T cells in an HIV+ subject (left) and their elimination 48h after KK10-SAP treatment (right). Numbers indicate %liveCD3+CD8+tetramer+ cells. **(B)** Viral inhibition assay showing loss of the suppressive capacity by KK10-zapped cells.

Conclusions: We have optimized a novel method to eliminate CTL of different specificities and thereby measure their individual contribution to viral suppression. This rapid, efficient, cost-saving method, applicable to any HLA type, will enable us to discriminate between the most efficacious and futile CTL responses in HIV infection and answer the long-standing question of the quality of different responses – the holy grail of a therapeutic HIV vaccine research.

363 Linking Pig-Tailed Macaque Major Histocompatibility Complex Class I Haplotypes and Cytotoxic T Lymphocyte Escape Mutations in SIV Infection

Shayarana Gooneratne[1]; Hamid Alinejad-Rokny[2]; Diako Ebrahimi Mohammadi[2]; Patrick Bohn[3]; Roger Wiseman[3]; David O'Connor[3]; Miles Davenport[2]; Stephen Kent[1]

[1]University of Melbourne, Melbourne, Australia; [2]University of New South Wales, Kensington, Australia; [3]University of Wisconsin Madison, Madison, WI, US

Background: Cytotoxic T lymphocytes select for virus escape mutants of HIV and SIV and this limits the effectiveness of vaccines and immunotherapies against these viruses. The influence of MHC-I alleles on HIV diversity has been well characterised in humans at the population level. MHC-I alleles likely affect viral diversity in the SIV-infected pig-tailed macaque (*M. nemestrina*) model, but this is poorly characterised. We studied the evolution of SIV in pig-tailed macaques with a range of MHC-I haplotypes.

Methods: SIVmac251 genomes were amplified from the plasma of 44 pig-tailed macaques infected with SIVmac251 at 4-10 months after infection and characterized by Illumina deep sequencing. MHC-I typing was performed on cellular RNA using Roche/454 pyrosequencing. MHC-I haplotypes and viral sequence polymorphisms were linked using in-house bioinformatics pipelines, both at individual mutations and groups of mutations spanning 10 amino acid segments, since CTL escape can occur at different amino acids within the same epitope in different animals.

Results: The approach successfully identified 6 known CTL escape mutations within 3 Mane-A1*084-restricted epitopes. The approach also identified over 70 new SIV polymorphisms linked to a variety of 32 MHC-I haplotypes. Using functional CD8 T cell assays we confirmed that one of these associations, a Mane-B028 haplotype-linked mutation in Nef, corresponded to a CTL epitope. We also identified mutations associated with the Mane-B017 haplotype that were previously described as CTL epitopes restricted by *Mamu-B*017:01* in rhesus macaques.

Conclusions: Patterns of immune escape variants are similar in HIV-1 infected human subjects that share the same MHC-I genes, but this has not been studied for SIV infection of macaques. By studying SIV sequence diversity in 44 MHC-typed SIV-infected pig-tailed macaques, we defined over 70 sites within SIV where mutations were common in macaques sharing particular MHC-I genes. Further, pig-tailed macaques sharing near-identical MHC-I genes with rhesus macaques responded to the same CTL epitope and forced immune escape. This allows many reagents developed to study rhesus macaque reagents to also be used to study pig-tailed macaques. Overall, our study defines sites of immune escape in SIV in pig-tailed macaques and this enables a more refined level of analysis of future vaccine design and treatment strategies for HIV.

364 HLA Class-II–Associated HIV Polymorphisms Predict Escape From CD4 T-Cell Responses

Nathaniel B. Erdmann[1]; Victor Du[1]; Jonathan M. Carlson[2]; John Sidney[3]; Ling Yue[4]; Susan Allen[4]; Eric Hunter[4]; Sonya L. Heath[1]; Anju Bansal[1]; Paul A. Goepfert[1]

[1]University of Alabama at Birmingham, Birmingham, AL, US; [2]Microsoft Research, Los Angeles, CA, US; [3]La Jolla Institute of Allergy and Immunology, La Jolla, CA, US; [4]Emory University, Atlanta, GA, US

Background: Human immunodeficiency virus (HIV) can escape antiretroviral therapy, antibody and CD8$^+$ T-cell pressure indicating these factors assist in viral control. The ability of CD4$^+$ T-cells to force escape mutations and influence HIV-1 viral control remains unclear.

Methods: We applied a computational approach to identify HIV polymorphisms (adaptations) in *gag*, *pol*, and *nef* disproportionately associated with specific HLA-II alleles in an African cohort of chronically infected individuals. Peptides including the predicted adaptation (AE) or a non-adapted version of the epitope (NAE) were synthesized and evaluated for immunogenicity. We applied a CD8$^+$-depleted interferon-γ ELISpot assay using PBMC obtained from chronically infected donors that were non-controllers (viral load >10,000 copies/mL), controllers (viral load <2,000 copies/mL) or acutely infected individuals. We determined the immunogenicity of predicted epitopes relative to dominant viral sequence in chronic infection, as well as transmitted founder virus (TFV) in acute HIV infection (AHI).

Results: We identified 29 HLA class-II associated HIV adaptations, all of which were demonstrated to represent novel CD4$^+$ T-cell epitopes. Consistent with a prior study, magnitude and breadth of HIV-specific CD4$^+$ T-cell responses seen in controllers was higher as compared to non-controllers. The magnitude of responses to epitopes containing the adapted polymorphism (AE) was lower when compared to NAE (p=0.0009). Even when the dominant viral sequence matched the predicted AE in chronic infection, NAE were more immunogenic (p=0.01). We studied a cohort of individuals with AHI to more clearly delineate the epitope responsible for observed immune responses. We found a relative lack of AE-specific CD4$^+$ T-cell responses (p=0.008) despite the TFV encoding equal numbers of AE and NAE. Longitudinal data from AHI individuals followed for 1-2 years off antiretroviral therapy demonstrated sequence changes at predicted epitopes that were biologically confirmed to represent CD4$^+$ T-cell mediated escape.

Conclusions: These data demonstrate the identification of HLA-II associated polymorphisms as a means to identify novel CD4$^+$ epitopes. In addition, our studies in acute and chronic infection definitively characterize HIV escape from CD4 T-cell responses, a phenomenon that is more common than previously anticipated. Our findings emphasize the importance of inducing CD4$^+$ T-cells along with CD8$^+$ T-cells and antibodies as part of a comprehensive HIV vaccine strategy.

365 Rapid Construction of HIV-1-Specific T Cell Receptor Gene Therapy Lentiviral Vectors

Christian Hofmann; Christian-Raul Aguilera-Sandoval; Arumugam Balamurugan; Priya Patel; Brian Diep; Edward Martin; Sangeun Park; Diana Y. Chen; Hwee Ng; Otto O. Yang
University of California Los Angeles, Los Angeles, CA, US

Background: HIV-1-specific CD8$^+$ cytotoxic T lymphocytes (CTL) can play an important role in the long-term control of HIV-1 replication *in vivo*. Unfortunately, most HIV-1-infected persons are unable to control the virus with their T cell receptor (TCR) repertoire, due to inadequate coverage of epitope variation. A potential immunotherapeutic strategy for a functional cure could be the adoptive transfer of gene-modified T cells, equipped with a combination of TCRs covering all common variants of their targeted epitope. We developed a rapid methodology to identify epitope-specific TCR sequences and insert them into lentiviral vectors without need for HLA tetramers, cell sorting, or cell cloning.

Methods: We focused on five HIV-1 Gag epitopes based on common or protective HLA type and epitope conservation: KRWIILGLNK$_{263-272}$ (KK10, HLA-B*2705), KAFSPEVIPMF$_{162-172}$ (KF11, B*5701), GLNKIVRMY$_{269-277}$ (GY9, B*1501), RQANFLGKI$_{429-437}$ (RI9, B*1302), and WASRELERF$_{36-44}$ (WF9, B*3501). Using a quantitative spectratyping method, we directly identified Gag-specific TCR sequences by expansion after epitope stimulation. Both TCR α and β chains were cloned in a one step reaction into a lentiviral vector. The functionality of these TCRs was examined through a Jurkat cell NFAT-dependent GFP reporter assay and also chromium release assays with transduced primary CD8$^+$ T cells against HIV-1-infected T1 cells transduced with the relevant HLA genes. Panels of HIV-1 NL4-3 with common epitope variants were generated by point mutagenesis.

Results: We cloned and functionally confirmed sixteen TCRs (seven for KK10, four for KF11, three for GY9, one for RI9, and one for WF9). Several TCRs have been screened for their recognition of epitope variants and functional avidity using synthetic peptides, and will be screened for their antiviral activity against cells infected with HIV-1 containing these variants.

Conclusions: Our data demonstrate proof-of-concept for rapid TCR cloning into vectors suitable for gene therapy and capacity to screen these TCRs for ability to recognize epitope variants. This sets the foundation for combination TCR gene therapy to cover epitope variation.

366 The Role of Exosomes in Semen in Suppressing Natural and Vaccine-Induced Immunity

Lucia Vojtech; Sean Hughes; Claire Levy; Florian Hladik
University of Washington, Seattle, WA, US

Background: Exposure to semen is the primary route of transmission for many sexually transmitted infections, including HIV. Accumulating evidence suggests that components in semen directly impair leukocytes, which could compromise the protective efficacy of vaccine-induced immune responses in the mucosa. Seminal plasma contains large numbers of extracellular microvesicles or exosomes (SE). Exosomes in general have been identified as important mediators of intercellular communication and immunoregulation. Thus, we explored the effects of SE on recipient blood and mucosal immune responses.

Methods: SE isolated from semen donated by healthy men were pooled from multiple donors. Dendritic cells (DCs) were derived from peripheral blood mononuclear cell (PBMC) monocytes. DCs and PBMC cultures were exposed to SE and assayed for SE uptake, immune function, and cytokine production by confocal microscopy, flow cytometry, Luminex, and quantitative PCR.

Results: Extracellular vesicles from semen are present at an average concentration of 2.2 x 10^{13} particles per ejaculate (n = 18 donors). These SE rapidly and efficiently entered peripheral and vaginal dendritic cells (DCs), more slowly entered B and CD4+ T cells, and only poorly entered CD8+ T cells. In PBMC cultures, SE impaired memory T cell function, reducing the production of TNF-alpha and/or IFN gamma in response to CMV, EBV, or influenza-derived peptides an average of 73% for CD4+ T cells and 55% for CD8+ T cells, in a dose-responsive manner (n = 4 donors). SE also impaired vaginal T cell responses to a superantigen. Exposing only DCs, as opposed to bulk PBMCs, to SE also blocked subsequent CD8+ memory T cell activation, reducing the proportion of cells making cytokines by 51% (n = 3 donors). This effect occurred even when only a fraction of DCs (as low as 20%) were exposed to SE. SE also impaired the innate immune response of monocytic THP-1 cells stimulated by bacterial lipopolysaccharide: cytokine production was reduced at both the mRNA level and the protein level.

Conclusions: SE inhibit a broad range of both innate and adaptive immune responses. CD4+ T cells appear to be directly affected, while CD8+ T cell function is impaired by affecting the co-stimulatory capacity of antigen-presenting cells. Understanding how programmed immune responses are altered by the presence of semen is important to developing the next generation of vaccines and preventative treatments against sexually transmitted diseases.

367 IFN-alpha Stimulated NK Lysis of HIV-Infected CD4$^+$ T Cells Requires NKp46 and NKG2D

Costin Tomescu[1]; Domenico Mavilio[2]; Luis J. Montaner[1]
[1]*The Wistar Institute, Philadelphia, PA, US;* [2]*Humanitas Clinical and Research Center, Milan, Italy*

Background: Interferon-alpha (IFN-alpha) is a potent clinical immuno-modulatory agent with the capacity to limit viral replication and stimulate NK activity against virally infected target cells. We have previously shown that NK lysis of HIV-1 infected autologous CD4$^+$ primary T cells requires *exogenous* IFN-alpha stimulation. Here, we identify the specific activating receptor(s) involved in HIV-1 infected target cell lysis by autologous NK cells activated *endogenously* with IFN-alpha.

Methods: Purified CD4$^+$ primary T cells were HIV-1 infected and used to stimulate IFN-alpha secretion from autologous PBMC. NK cell-mediated cytotoxicity was measured with a 4 hour chromium release assay in the presence or absence of neutralizing monoclonal antibodies against 2B4, NTB-A, NKG2D, NKp30, NKp44, and NKp46. Comparisons of three or more paired groups was carried out using a Friedman test adjusted with post-hoc analyses of two groups by a Wilcoxon signed-rank test.

Results: Direct recognition of HIV-1 infected target cells by autologous PBMC led to the secretion of significant amounts ($p<0.001$) of IFN-alpha by Plasmacytoid Dendritic Cells. *Endogenous* IFN-alpha stimulation led to strong NK activation as detected by CD69 upregulation and triggered NK lysis of HIV-1 infected autologous CD4$^+$ primary T cells ($p<0.01$). IFN-stimulated NK cell lysis of HIV-1 infected CD4$^+$ primary T cells was significantly decreased in the presence of neutralizing antibodies against NKp46 ($p<0.01$) and NKG2D ($p<0.05$) while NKp30, NKp44, 2B4 and NTB-A were not required.

Conclusions: The NKp46 and NKG2D activating NK cell receptors are required for NK lysis of HIV-1 infected autologous CD4$^+$ primary T cells following IFN-alpha stimulation. The anti-viral mechanisms of action of IFN-alpha against HIV-1 may in part be due to NK-mediated clearance of HIV-1 infected target cells via the NKp46 and NKG2D receptors.

TUESDAY, FEBRUARY 24, 2015

Session P-F1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Immune-Based Strategies in Latency

368 Stimulation of Broad CTL Response Is Required to Clear Latent HIV-1 in Humanized Mice

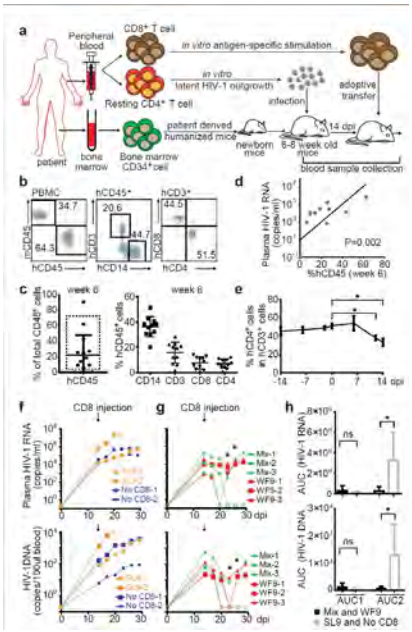
Liang Shan[1]; Kai Deng[2]; Richard Flavell[1]; Robert F. Siliciano[2]

[1]*Yale University, New Haven, CT, US;* [2]*Johns Hopkins University School of Medicine, Baltimore, MD, US*

Background: Despite antiretroviral therapy (ART), HIV-1 persists in a stable latent reservoir, primarily in resting memory CD4$^+$ T cells.To purge the reservoir, pharmacological reactivation of latent HIV-1 has been proposed and tested both *in vitro* and *in vivo*. The next step is to eliminate the resting CD4$^+$ T cells in which latent HIV-1 has been induced through virus-specific immune mechanisms including cytolytic T lymphocytes (CTL). However, the vast majority (>98%) of latent viruses in chronic patients carry CTL escape mutations that render the infected cells insensitive to CTLs directed at common epitopes, such as SL9 epitope in HLA-A2-positive patients.

Methods: To test whether CD8$^+$ T cells from patients under ART are able to recognize and clear latent HIV-1, we generated patient-derived humanized mice using a recently reported mouse system named MISTRG. With humanization by knockin replacement of the *Csf1*, *Csf2, Il3, Tpo* and *Sirpa* genes in the *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$ genetic background, MISTRG mice are highly permissive for human hematopoiesis and support the reconstitution of robust human lymphoid and myelomonocytic systems. We infected patient-derived humanized mice with primary HIV-1 isolates grown from resting CD4$^+$ T cells of the same patient and then evaluated antiviral effect of autologous CD8$^+$ T cells.

Results: MISTRG mice engrafted with HLA-A2-positive patient bone marrow CD34$^+$ cells successfully developed human T-lymphocyte and monocyte/macrophage subsets, which were sufficient to support HIV-1 infection. In control mice or mice that received autologous patient CD8$^+$ T cells pre-stimulated with the common epitope SL9, levels of plasma HIV-1 RNA and proviral DNA in PBMCs continued to increase from day 14 to day 29 after infection. In sharp contrast, 100- to 1,000-fold decreases in plasma HIV-1 RNA levels were observed in all mice that received patient CD8$^+$ T cells pre-stimulated with the mixture of Gag peptides including unmutated epitopes.



Broad-spectrum cytotoxic T lymphocytes suppress in vivo infection of patient-derived humanized mice with autologous latent HIV-1**.**

Conclusions: Our results demonstrate that chronically infected patients retain a broad spectrum viral-specific CTL response which is sufficient to inhibit in vivo replication of HIV-1 isolated from latent reservoir. These results suggest that latent HIV-1 can be eliminated in chronically infected patients despite the overwhelming presence of CTL escape variants. Directing efficient CTL responses to unmutated viral epitopes is essential to the clearance of latent HIV-1.

369 *In vivo* effects of Panobinostat and Romidepsin on HIV-1-specific CD8 T Cell Immunity

Rikke Olesen[1]; Thomas A. Rasmussen[1]; Mathias Lichterfeld[2]; Mette E. Graversen[1]; Steffen Leth[1]; Lars Østergaard[1]; Ole S. Søgaard[1]; Martin Tolstrup[1]

[1]*Aarhus University Hospital, Aarhus, Denmark;* [2]*Ragon Institute of MIT, MGH and Harvard, Boston, MA, US*

Background: We recently showed that the histone deacetylase inhibitors (HDACi) panobinostat (PANO) and romidepsin (ROMI) activates HIV-1 from latency in HIV-1 infected patients on antiretroviral therapy (ART). However, concern has been raised that HDACi may diminish effector functions of CD8 T cells, thus impairing the elimination virus-expressing cells. Here, we evaluated HIV-1-specific CD8 T cell responses during clinical administration of PANO and ROMI.

Methods: In two separate clinical trials, PANO (20 mg per dose) or ROMI (5mg/m^2 per dose) were administered to virologically suppressed HIV-1 infected adults on ART. In 14 of 15 PANO-treated and 6 of 6 ROMI-treated patients, cryo-preserved PBMCs isolated pre-HDACi (baseline), on-HDACi, and post-HDACi (follow-up) were analyzed by intracellular cytokine staining (ICS) following stimulation with a HIV-1 Gag peptide pool. Cells were labelled with Near-IR amino reactive dye, surface antibodies (CD4, CD8, CD45RA and CCR7) and IFNγ (ICS) and analyzed on a BD FACSVerse cytometer. Comparisons were performed using Wilcoxon matched-pairs test.

Results: We observed no overall statistical significant changes in total CD8 T cell counts before and after PANO or ROMI treatment. However, during PANO treatment the relative composition of CD8 T cell subsets changed significantly with increased proportions of effector memory (EM) (p=0.005) and central memory CD8 T cells (p=0.03); and decreased proportions of naïve CD8 T cells (p=0.04). These changes had returned to pre-HDACi levels at follow-up. During ROMI treatment we saw no statistical significant change in the CD8 T cell memory subset composition. The majority of HIV-specific cells in all subjects were EM CD8 T cells. In 11 of 14 (79%) PANO-treated patients and 5 of 6 (83%) ROMI-treated

patients, we detected IFNγ+ HIV-specific EM CD8 T cells. In these patients, the mean IFNγ+ HIV-specific EM CD8 T cell responses were 0.80% (range 0.12-2.39%) and 0.95% (range 0.86-4.32%) at baseline for PANO- and ROMI-treated subjects, respectively. The frequency of IFNγ+ HIV-specific EM CD8 T cell responses did not change during PANO (p=0.7) or ROMI (p=0.1) treatment or at follow-up (PANO p=0.7, ROMI p=0.8).

Conclusions: In two clinical trials, treatment of HIV-1 infected patients with PANO or ROMI did not decrease the levels of HIV-1-specific EM CD8 T cells. These results provide support for the combination of HDACi and immune-based therapies in HIV-1 eradication trials.

370 Vaccine Induced Follicular CD8 T Cells Enhance Control of Pathogenic SIV Infection

Geetha H. Mylvaganam; Daniel Rios; Gregory Tharp; Steven Bosinger; Vijayakumar Velu; Rama R. Amara
Emory University, Atlanta, GA, US

Background: Recent data demonstrated that a significant fraction of latently-infected cells reside in the germinal center (GC) resident T follicular helper cells (Tfh) during HAART of HIV-infected humans/SIV-infected macaques. Therapeutic interventions aimed at achieving a functional cure must target these viral reservoirs. Induction of highly functional anti-viral CD8 T cells that can home to GC (follicular CD8) represents an attractive therapeutic strategy. However, GCs are generally thought to exclude CD8 T cells and very little is known about whether T cell based vaccines induce anti-viral CD8 T cells with the potential to migrate to the GC and influence HIV/SIV replication in Tfh. Here, we addressed this in the context of DNA/MVA vaccination and pathogenic SIV infection in rhesus macaques (RM).

Methods: RM were vaccinated with our DNA/MVA SIV vaccine with and without adjuvants and challenged intrarectally with SIVmac251. Follicular CD8 T cells were identified based on the expression of chemokine receptor CXCR5 (B cell follicle homing potential) on Gag CM9 tetramer+ CD8 T cells (Tet+).

Results: Following vaccination, a small fraction (<10%) of Tet+ CD8 T cells in blood expressed CXCR5. However, following SIV infection, the frequency of Tet+ CXCR5+ CD8 T cells in blood and LN increased dramatically as early as 2 weeks post infection, were present at high levels even at 24 weeks (about 40% of Tet+ in LN) and correlated directly with their frequency post vaccination. These Tet+ CXCR5+ cells were not present in unvaccinated SIV infected animals although Tet+ cells were present. Importantly, among the vaccinated animals the frequency of Tet+ CXCR5+ CD8 T cells in blood at 2 weeks post infection was strongly associated with enhanced viral control both at peak and set point. Immunofluorescence staining of both rectal and LN tissues from vaccine controllers revealed co-localization of CD8 T cells with Tfh in GC. Impressively, the CXCR5+ CD8 T cells from the controller RM restricted the anti-CD3 driven expansion of CM9 peptide pulsed Tfh cells in vitro suggesting their killing potential. Transcriptome analysis of purified CXCR5+ Tet+ CD8 T cells identified these cells as a unique multi-faceted population expressing genes associated with both CTLs and Tfh subsets.

Conclusions: Our results demonstrate that it is possible to elicit follicular CD8 T cells by vaccination and these cells contribute significantly to the control of SIV infection. These findings have implications for cure strategies against HIV.

371 Blockade of PD-L1 Does Not Reverse HIV Latency in CD4+ T Cells Ex Vivo

Elizabeth Fyne[1]; Shalyn Campellone[2]; Huilin Qi[2]; Amy Sheaffer[2]; Stephen Mason[2]; John W. Mellors[1]
[1]*University of Pittsburgh, Pittsburgh, PA, US;* [2]*Bristol-Myers Squibb Co., Wallingford, CT, US*

Background: Blockade of the PD-1/PD-L1 pathways using monoclonal antibodies (mAb) to PD-1 has been reported to activate HIV expression from latently infected CD4 T cells ex vivo. To further evaluate this approach, we tested the ability of the human anti-PD-L1 mAb BMS-936559 to activate virion production from mononuclear cells obtained from patients on suppressive ART.

Methods: PBMC, total (t) CD4, and resting (r) CD4 cells were purified by negative selection of large-volume blood draws from HIV-infected donors. Freshly isolated PBMCs were cryopreserved and immunophenotyped for PD-1/PD-L1 expression. The remaining cells were incubated (1 million cells/well in triplicate) for 1 week with 20, 5, or 1.25μg/ml anti-PD-L1 mAb, with 20μg/ml isotype control [Zymogen DT-1D12g-4P (hIgG4)], or with anti-CD3/CD28-coated microbeads plus either anti-PD-L1 mAb or isotype control. On Day 8, cells were assessed for viability and supernatants tested for HIV RNA using the Roche Taqman v.2.0. A virologic response was defined as a >3-fold increase in HIV RNA over isotype control. Donors whose cells responded initially to anti-PD-L1 mAb were redrawn and tested again.

Results: PBMC, tCD4, and rCD4 cells purified from ten long-term (mean 8 years) suppressed donors. Cell viability was not reduced by treatment with anti-PD-L1 mAb. 9 of 10 donors responded to anti-CD3/CD28 in all cell types (mean fold-increases of 742, 1353, and 272 for PBMC, tCD4 and rCD4, respectively). Anti-PD-L1 mAb did not enhance responses to anti-CD3/CD28. PBMC from 2 of 10 donors (donor 3: 61-fold; donor 4: 7-fold) showed an initial response to anti-PD-L1 mAB that was not reproduced upon repeat blood draw. tCD4 cells from 2 of 10 donors (donor 2: 583-fold; donor 6: 84-fold) initially responded to anti-PD-L1. However, cells from donor 2 did not respond after a repeat draw. Cells from donor 6 responded on the first repeat draw but not the second. rCD4 from 0 of 10 donors responded to anti-PD-L1. PD-1/PD-L1 expression on CD4 and CD8T cells was evident on the day of cell isolation in all donors, but expression levels did not differ between responders, non-responders, and a healthy control.

Conclusions: Despite detectable PD-1/PD-L1 expression, increased HIV production from PBMC, total CD4 T cells or resting CD4 T cells after treatment with anti-PD-L1 antibody was infrequent and not reproduced longitudinally. Alternate strategies will be needed to activate proviral expression from latently infected CD4 T cells.

372 Impact of HIV Latency Reversing Agents on Natural Killer Cells

Carolina Garrido; Julia Sung; Swati Gupta; Katherine Sholtis; Nancie Archin; David Margolis
Medicine, University of North Carolina
University of North Carolina, Chapel Hill, NC, US

Background: Eradication of HIV infection requires unmasking of the HIV latent reservoir using latency reactivating agents (LRAs) and the implementation of an immune response to clear infected cells. Thus, an assessment of the impact of LRAs immune function is required. We evaluated the effect of LRAs on natural killer cells (NKs).

Methods: Five LRAs were evaluated: 3 histone deacetylase inhibitors, SAHA, Romidepsin (RMD) and Panobinostat (PNB); and 2 protein kinase C activators, Prostratin (PRT) and Ingenol (ING). Each drug was tested at 3 concentrations (cc): physiological, lower and higher. NKs from 3 HIV-negative donors were isolated and exposed 24h to the LRAs and washed out. NKs viability was assessed by AnnexinV+7AAD staining. Cytotoxicity was evaluated through degranulation upon culture with K562 cells, measuring %$CD56^+CD107a^+$cells. Antiviral activity was measured in a viral inhibition assay using autologous $CD4^+$T cells infected with JR-CSF and quantifying p24 at day 7 of culture.

Results: Table 1 shows results for LRAs treatment at physiological concentration. RMD, PNB and PRT showed significant toxicity on NKs. Of note, SAHA and ING did not increase cell death at any cc, while PNB produced significant cell death even at lower cc (5nM) (261.9% (63.8)). RMD, PNB and ING at physiological cc reduced significantly degranulation, and we observed an increase of both viability and degranulation impairment at higher cc (100, 100 and 1000 nM, respectively) of these drugs. Viral inhibition assays showed that any cc of SAHA impair antiviral activity, while RMD impaired it significantly at physiological and lower cc (68.8%(10.6)). Interestingly, ING had a bimodal effect, impairing viral inhibition (28.6% (9.5)) at low cc but improving it at higher cc (183.2% (91.1)). All other conditions did not produce statistically significant differences compared to untreated NKs, but we observed that PRT did not impair viral inhibition while PNB at physiological cc reduced NK antiviral effect to 37.46% (40.72).

	Untreated NKs	SAHA (335 nM)	RMD (10 nM)	PNB (20 nM)	PRT (1000 nM)	ING (100 nM)
AnnexinV+7AAD+	100	123.1 (14.5)	192.9* (35.3)	261.9* (63.8)	114.7* (6.6)	95.9 (3.7)
CD56+CD107a+	100	103.1 (2.3)	80.0* (2.5)	55.8* (3.1)	86.8 (4.5)	66.6* (7.1)
% HIV inhibition	100	131.1 (14.23)	35.9* (8.54)	37.46* (23.51)	110.26 (27.81)	51.93* (21.11)

Table 1. Toxicity, degranulation and antiviral activity of NKs treated with the different LRAs at physiological concentration, compared to NKs without treatment. Mean (SEM). * indicates significance (p<0.05, paired t test)..

Conclusions: RMD and PNB impaired viability, cytotoxicity and antiviral activity of NKs at physiological concentrations. PRT and ING had a modest effect on NK function. SAHA did not show any effect on NKs at the tested concentrations. This in vitro data indicates that some LRAs can impair NK immune function, and thus could have an impact on viral clearance after reactivation. However, in vivo testing is warranted to fully understand how these LRAs impact in the immune system when all components are present.

THURSDAY, FEBRUARY 26, 2015

Session P-F2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Viral Reservoir Dynamics During ART

373 The Earlier cART Is Initiated During PHI, the More Intracellular HIV-DNA Decreases

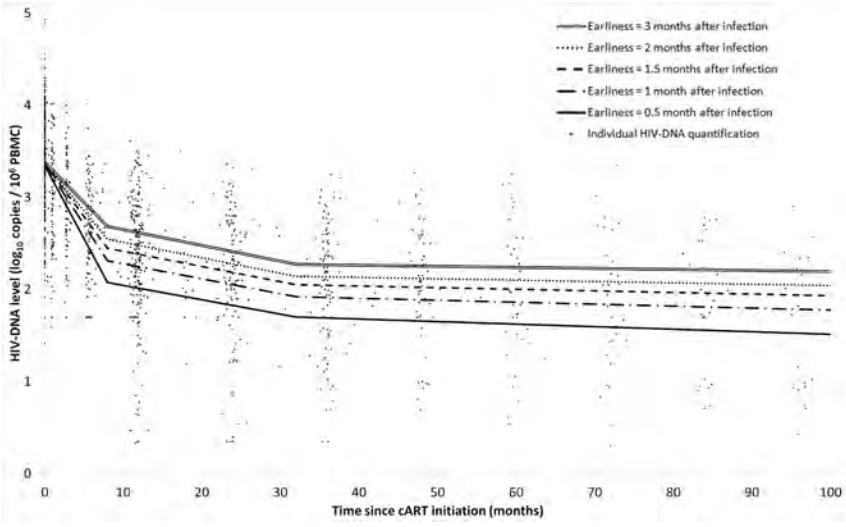
Moussa Laanani[2]; Jade Ghosn[1]; Asma Essat[2]; Adeline Mélard[3]; Rémonie Seng[2]; Emmanuel Mortier[4]; Cécile Goujard[2]; Laurence Meyer[2]; Christine Rouzioux[3]
On behalf of the ANRS PRIMO Cohort Study Group

[1]APHP, Hôtel Dieu University Hospital, Paris, France; [2]APHP, Bicêtre Hospital, Le Kremlin-Bicêtre, France; [3]APHP, Necker Hospital, Paris, France; [4]APHP, Louis Mourier Hospital, Colombes, France

Background: During the earliest weeks of primary HIV infection (PHI), HIV establishes a reservoir mainly in CD4+ T cell subsets. Combined antiretroviral therapy (cART) initiation during PHI yielded better immune restoration and larger decrease in cell-associated HIV-DNA than initiation during the chronic phase. In macaques, the reduction of SIV-DNA reservoir under cART was greater when initiated between 7 and 10 days than between 10 and 42 days after infection. Our objective was to model the short- and long-term decay of the cell-associated HIV-DNA blood reservoir in patients initiating cART during PHI and to assess the impact of the earliness of cART initiation on HIV-DNA level decay.

Methods: We included patients enrolled during primary HIV-1 infection in the multicenter ANRS PRIMO cohort, treated within the month following enrollment and achieving sustained virological response (HIV-RNA <50 cp/mL) as from Month 6. The decay of cell-associated HIV-DNA over time while on successful cART was modeled with a 3-slope linear mixed-effects model.

Results: 327 patients were included, accounting for 1,305 HIV-DNA quantifications**.** Median time between infection and cART initiation was 41 days (IQR: 33-54), and median follow-up under uninterrupted cART was 2.3 years (range: 0.4-16.6). The impact of the earliness of cART initiation was statistically significant on the first slope ($p<0.0001$): the earlier cART was initiated after HIV infection, the faster the HIV-DNA level decreased during the first 8 months of cART: -0.171, -0.131, and –0.068 $\log_{10}$ copies/10^6 PBMC /month when cART was initiated 15 days, 1 month, and 3 months after infection, respectively. The HIV-DNA level continued to decrease significantly under cART after Month 8 but with a lower steepness, and the second and third slopes were similar regardless of cART initiation earliness. The predicted mean HIV-DNA level achieved after 5 years of uninterrupted successful cART was 1.62 $\log_{10}$ copies/10^6 PBMC when cART was initiated 15 days after infection, and 2.24 $\log_{10}$ copies/10^6 PBMC when cART was initiated 3 months after infection ($p=0.0006$). Similar impact of cART earliness on HIV-DNA decrease was found when using the number of antibodies on western blot assay performed at cART initiation as a measure of precocity.



Slopes of decay of HIV-DNA under uninterrupted cART with successful virological response (<50 copies/ml from 6 months) predicted by a mixed-effects model, according to cART initiation earliness from HIV infection: the ANRS PRIMO cohort (327 patients, 1,305 measurements)

Conclusions: This study provides strong arguments in favor of cART initiation at the earliest possible time point after HIV infection. It also adds further weight for promoting early HIV diagnosis.

374 Decay Rate and HIV-1 DNA Reservoir Size Following Early Infant Antiretroviral Therapy

Priyanka Uprety[1]; Kaitlin Rainwater-Lovett[2]; Ellen G. Chadwick[3]; Edmund Capparelli[4]; Carrie Ziemniak[2]; Katherine Luzuriaga[5]; Larry Moulton[1]; Deborah Persaud[2]
International Maternal Pediatric Adolescent AIDS Clinical Trial Network (IMPAACT) P1030 trial group

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [4]University of California San Diego, San Diego, CA, US; [5]University of Massachusetts Medical School, Boston, MA, US

Background: In a perinatally HIV-infected child, ART at 30 hours of life was associated with reduced human immunodeficiency virus (HIV) reservoirs and 27 months of virologic remission. Knowledge of infected cell frequencies and decay as a function of age at ART is important for informing clinical trials aimed to study these effects.

Methods: 18 perinatally HIV infected infants in a multicenter, open-label, phase I/II, trial of lopinavir+ritonavir-based ART (IMPAACT P1030 trial) initiated before (early-treated [ET]) or after (late-treated [LT]) 6 weeks (wks) of age were studied. Infants with available samples (n=18) were included in the study if they either achieved a 2-log viral load (VL) decrease from baseline and sustained VL<400 by 48 weeks or achieved and maintained VL to <400 by 24 weeks.Total PBMC HIV DNA and 2-LTR circles were quantifed by droplet digital PCR (<3 copies/million (c/m) at baseline, 24, 48, and 96 wks of ART and linear decay rates were estimated for each infant. Total HIV DNA was correlated with age at ART, and HIV DNA levels during ART. All data are reported as mean and 95% confidence interval, except for age of ART which is reported as median and range.

Results: The median age of ART initiation was 5.71 (4.30-5.86) and 11.14 (6.86-23.43) wks for ET (n=5) and LT (n=13) infants, respectively. Before ART, HIV DNA in ET and LT was 3.16 [2.53, 3.78] and 3.27 [2.80,3.73] $\log_{10}$ copies/million (c/m) (p=1.00). Overall, HIV DNA decayed faster in ET vs. LT (-0.034 [-0.054,-0.015] vs. (-0.017 [-0.022, -0.013] $\log_{10}$ c per wk; p=0.03). From 0 to 24 wks of ART, HIV DNA decreased by 1.25 [0.96,1.55] and 0.89 [0.75,1.02] $\log_{10}$ c/m in ET and LT, respectively (p=0.008), but did not differ between groups from 24 to 48 wks (p=0.58). After 48 weeks of ART, there was a trend towards lower HIV DNA in ET vs. LT (1.26 [-0.19,2.71] vs. 2.11 [1.51, 2.71] $\log_{10}$ c/m; p=0.08). Overall, HIV DNA load at baseline was highly correlated with HIV DNA load at 24, 48 and 96 wks of ART (p<0.001). 2-LTR circles were detectable at baseline in 80% and 77% (p=1.00), at 24 weeks in 25% and 83.4% (p=0.12) and at 48 weeks in 0% and 80% (p=0.03) of ET and LT infants, respectively.

Conclusions: Earlier initiation of ART did not substantially affect pre-ART infected cell frequencies but was associated with faster HIV decay. However, HIV-1 DNA burden established before initiation of ART determined the DNA reservoir during suppressive ART.

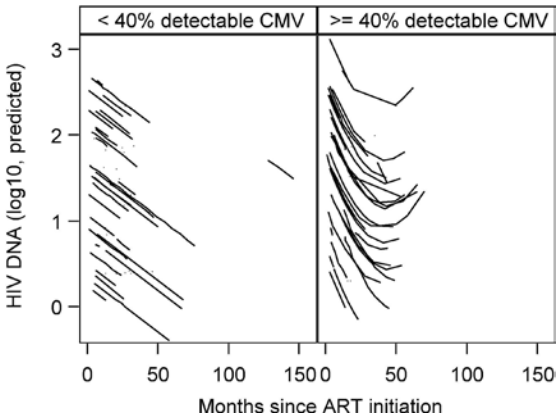
375 Detectable CMV in PBMC Is Associated With Slower HIV DNA Decay During Suppressive ART

Sara Gianella Weibel; Christy Anderson; Susanna R. Var; Michelli Faria de Oliveira; Marta Massanella; Susan J. Little; Douglas D. Richman; Matt Strain; Josue Pérez-Santiago; David M. Smith
University of California San Diego, La Jolla, CA, US

Background: Asymptomatic CMV replication is frequent in HIV infected men, and is associated with increased immune activation, T cell proliferation and HIV disease progression. We hypothesized that persistent CMV replication influenced HIV DNA dynamics after initiation of antiretroviral therapy (ART) during early HIV infection.

Methods: We investigated 397 peripheral blood mononuclear cell (PBMC) samples collected from 96 CMV-seropositive, recently HIV-infected men. Participants started ART within a median of 5 months from estimated date of infection (EDI) (range: 0-8), achieved suppressed HIV RNA in blood within a median of 6 months on ART (range: 1-8) and were followed for a median of 17 months after ART start (range: 12-75). The median CD4 count at presentation was 485 cells/μl and the median peak HIV RNA was 4.8 $\log_{10}$ HIV RNA cp./ml. Levels of CD4-associated HIV DNA and CMV DNA were measured by droplet digital PCR for each time-point (mean 4 TP/participant). Using a general linear mixed-effect regression model, associations between HIV DNA decay, age, frequency of detectable CMV, nadir CD4 count, peak HIV RNA level, time from EDI to ART start, and time from ART start to virologic suppression were evaluated.

Results: Higher peak HIV RNA levels and higher frequency of detectable CMV in PBMC (>40% of sampled time-points) were associated with increased levels of HIV DNA during ART (p<0.01). Both factors were independently associated with higher HIV DNA in multivariable analysis (p<0.01). No other variable contributed significantly. The pattern of HIV DNA decay during ART differed significantly between participants with higher versus lower frequency of detectable CMV in PBMC (> vs < 40% of samples with detectable CMV). When considered separately, a linear model had a significantly better fit for HIV DNA decay in the low-frequency CMV group, while a quadratic model of HIV DNA decay had a better fit for participants with higher frequency of CMV DNA (p<0.01, see figure). In other words, individuals with more detectable CMV demonstrated a U-shaped pattern of HIV DNA decay while the low frequency CMV group had a linear pattern of decay.



When considered separately, a linear model had a significantly better fit for HIV DNA decay in the low-frequency CMV group (<40% detectable CMV, left panel), while a quadratic model of HIV DNA decay had a better fit for participants with higher frequency of CMV DNA (>40% detectable CMV, right panel).

Conclusions: Detectable CMV DNA in PBMC is associated longitudinally with higher HIV DNA levels, even among individuals who started ART early during HIV infection, suggesting that CMV replication may help maintain the stability of the HIV DNA reservoir. Future studies with anti-CMV therapeutics could help determine underlying mechanisms and if causal associations exist.

376 Stable Total HIV-1 DNA Levels Prior and Post ART Interruption in Chronic HIV

Emmanouil Papasavvas[1]; Matthew Strain[2]; Steven Lada[2]; Jocelin Joseph[1]; Livio Azzoni[1]; Karam Mounzer[3]; Jay R. Kostman[4]; Douglas D. Richman[2]; Luis J. Montaner[1]

[1]The Wistar Institute, Philadelphia, PA, US; [2]VA San Diego Healthcare System and the University of California, San Diego, CA, US; [3]Jonathan Lax Immune Disorders Treatment Center, Philadelphia Field Initiating Group for HIV-1 Trials, Philadelphia, PA, US; [4]Presbyterian Hospital–University of Pennsylvania Hospital, Philadelphia, PA, US

Background: The persistence of the HIV reservoir during antiretroviral therapy (ART) is a barrier to HIV eradication. The impact of viremic episodes on cell-associated HIV DNA or RNA in the context of ART-mediated suppression remains unknown.

Methods: Peripheral blood mononuclear cells (PBMC) from 23 ART-suppressed, chronically HIV-1-infected subjects were evaluated at initiation of treatment interruption (TI, baseline), during HIV viremia soon after TI, and following ART-mediated HIV viral load (VL) re-suppression for: a) T cell activation [CD38, HLA-DR, CD28, CD95 and TNFRII expression on $CD4^+$ or $CD8^+$ T cells] by flow cytometry, and b) viral measures including: i) cell associated HIV DNA [total HIV DNA (pol copies) and episomal 2-long terminal repeat (2-LTR) circles] by droplet digital PCR (ddPCR), and ii) cell associated HIV unspliced (gag), multi spliced RNA (tat/rev) and poly-A tailed transcripts (PolyA), by reverse transcriptase-ddPCR. Differences between time points were tested using Wilcoxon Signed-Rank or paired t-tests. Correlations were assessed using Spearman tests. All statistics used JMP Pro11.

Results: The median HIV VL during TI [median time=4 weeks, interquartile range (IQR)=4-9] was 72900 copies/ml (IQR=32558-127193). When compared to pre-TI levels, TI resulted in a decrease in $CD4^+$ T cells/mm^3 ($p<0.0001$), increase in T cell activation [e.g. $CD8^+CD38^+$ percent $p=0.0005$], and increase in cell associated HIV DNA (pol $p<0.0001$, 2-LTR $p=0.0362$) and RNA (gag $p<0.0001$, tat/rev $p<0.0001$, PolyA $p<0.0001$). Upon resumption of ART, HIV re-suppression occurred after a median of 16 weeks (IQR=12-22) and resulted in restoration of $CD4^+$ T cells/mm^3, reduction of T cell activation, and return of total HIV DNA and cell-associated HIV RNA to pre-TI levels. However, levels of activated (e.g. $HLA\text{-}DR^+$) $CD4^+$ T cells and 2-LTR circles remained higher than pre-TI levels ($p=0.0171$ and $p=0.0323$, respectively) even after viral re-suppression. Pre-TI mean fluorescent intensity of CD38 on $CD4^+HLA\text{-}DR^+$ T cells was positively associated with total HIV DNA levels observed during TI ($p=0.034$, $Rho=0.4437$) and after viral re-suppression ($p=0.0289$, $Rho=0.4658$).

Conclusions: ART-mediated HIV VL re-suppression restored total HIV DNA to pre-TI levels, but retained higher 2-LTR levels. In addition, pre-TI T cell activation levels were positively correlated with total HIV DNA levels observed during TI and following viral re-suppression.

377 Aviremia 10-Year Post-ART Discontinuation Initiated at Seroconversion

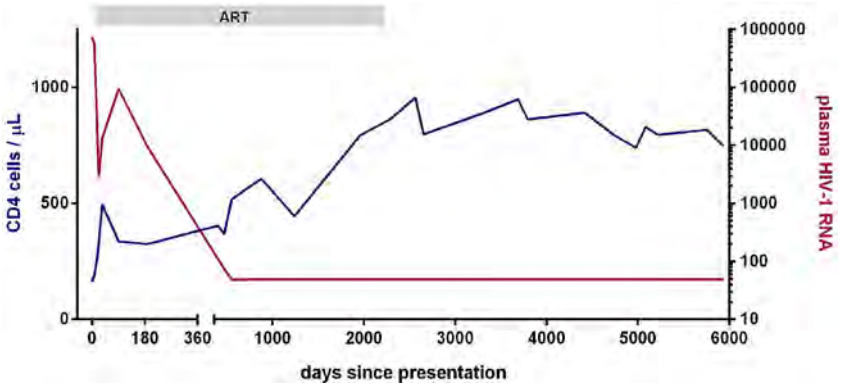
Sabine I. Kinloch[1]; Lucy Dorrell[2]; Hongbing Yang[2]; Linos Vandekerckhove[3]; Ward de Spiegelaere[3]; Eva Malatinkova[3]; Sabine Yerly[4]; Daniel Webster[5]; Margaret Johnson[5]

[1]University College London, London, United Kingdom; [2]University of Oxford, Oxford, United Kingdom; [3]Universitair Ziehenhuis Gent, Gent, Belgium; [4]Geneva University Hospital, Geneva, Switzerland; [5]Royal Free London NHS Foundation Trust, London, United Kingdom

Background: Early ART initiation is associated with impact on HIV-1 reservoir establishment and decay with the potential for virological control post-treatment discontinuation. Underlying mechanisms of post-virological control remain unclear.

Methods: We report on a clade C-infected female patient who has maintained undetectable viremia for 10 years after stopping a 6-year treatment period initiated at PHI with initial virological failure while on ART and describe her virological parameters and HIV-1 specific T cell responses.

Results: A 23-year-old female seroconverted with a 3-week long severe acute retroviral syndrome in October 1997. Baseline characteristics and follow-up viral load (VL) and CD4 T cells data are shown on **Figure.** Compromised viro-immunological parameters with CD4 <200 cells/mm^3 on 3 occasions and VL >750,000 HIV-1 copies(c)/mL (clade C) were present before ART initiation on 20.10.97 (AZT-3TC-indinavir 800 mg tds switched to ritonavir 600 mg bd 2 weeks later). Failure of this regimen up to 94,000 c/mL prompted treatment intensification and aviremia was achieved in April 1999. ART was maintained until January 2004 followed by aviremia for 10 years with preservation of CD4 T cells and CD4/CD8 ratio>1 **(Figure).** HLA genotype was not one generally associated with a favorable outcome. At 10 years of aviremia (2014), total HIV-1 DNA, integrated HIV-1 DNA and 2-LTR circles were 148.93 (95% CI: 76.99 - 229.64), 134.31 (95% CI: 56.47 – 304.39) and 3.89 (95% CI: 0 - 9.15) HIV-1 copies/million PBMCs, respectively. CD4 and CD8 HIV-1 specific T cell responses showed moderately potent CD8+ T cell inhibition of a clade-matched HIV-1 isolate equivalent to that which we have observed in ART-naïve chronically infected subjects with VL set-point <10,000 HIV-1 copies/mL. Unusually broad gag-specific IFN-γ CD4 responses were detected, of note, targeting multiple regions of genetic vulnerability that are associated with virological control.



Conclusions: Persistence of intermediate levels of total and integrated HIV-1 DNA and broad HIV-1 gag-specific CD4 T cell responses, together with preserved CD8+ T cell viral inhibitory activity were associated with prolonged aviremia post-stopping treatment, suggesting that further insight into CD4 T cells should be gained in terms of the mechanisms underlying virological control post-ART.

378 Identifying HIV Variants that Rebound after Treatment Interruption

Mary F. Kearney[2]; Wei Shao[3]; Rajesh T. Gandhi[4]; Brandon F. Keele[3]; **Jonathan Z. Li**[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [2]National Cancer Institute (NCI), Frederick, MD, US; [3]Frederick National Laboratories for Cancer Research, Frederick, MD, US; [4]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

Background: Our knowledge of the source of rebounding HIV after analytic treatment interruption (ATI) is limited. Understanding the origin of HIV variants during early rebound would provide insight into the composition of the HIV reservoir and has implications for the design of curative interventions. We examined HIV single-genome sequences (SGS)

of ten AIDS Clinical Trials Group (ACTG) participants who underwent an ATI and compared their rebounding virus with those from pre-ART plasma, and latent and expressed HIV reservoirs as defined by on-ART PBMC cell-associated DNA and RNA (CA-DNA and CA-RNA).

Methods: Ten ACTG participants were identified who enrolled in a first-line ART initiation study and subsequently participated in an ATI study while on suppressive ART. SGS were obtained from pre-ART plasma, PBMCs collected during virologic suppression, and from early post-ATI plasma. The genetics of the HIV populations at each time point and in each compartment were compared phylogenetically and using tests for panmixia. Sequence diversity was calculated by average pairwise distance (APD).

Results: PBMCs were collected a median of 4 years after ART initiation and post-ATI plasma were obtained a median of 1 week after initial detectable viremia with a median viral load of 17,286 HIV RNA copies/mL. A median of 25 SGS were obtained from each participant time point. Despite many years of suppressive ART, the viral diversity of on-ART CA-RNA and CA-DNA were similar to that of the pre-ART plasma HIV RNA (median APD of CA-RNA vs. CA-DNA vs. pre-ART plasma RNA: 1.1% vs. 1.2% vs. 1.2%, repeated measures ANOVA P=0.70). Hypermutated HIV sequences were detected in both CA-DNA and CA-RNA. For most participants, the oligoclonal populations of rebounding HIV were found to have a population structure not significantly different than HIV from pre-ART and on-ART samples, although the rebounding virus were most closely related to either CA-RNA or CA-DNA. In one instance, we found CA-RNA that closely matched rebound viremia. The diversity of pre-ART plasma HIV RNA in this participant was low (0.23%), indicating that treatment may have been initiated early after infection.

Conclusions: HIV diversity in the latent and expressed PBMC HIV reservoirs were similar to that found in pre-ART plasma RNA despite several years of ART. In some cases, early rebound virus closely matched those found in the expressed PBMC HIV reservoir, but in other cases, rebounding HIV may have originated from sources other than circulating PBMCs.

379 Characterizing the Active HIV Reservoir on ART: Cell-Associated HIV RNA and Viremia

Feiyu Hong; Elizabeth Fyne; Anthony R. Cillo; Margaret A. Bedison; Dianna Koontz; John W. Mellors
University of Pittsburgh, Pittsburgh, PA, US

Background: Despite combination antiretroviral therapy (ART), HIV-1 RNA can be detected in plasma and peripheral blood mononuclear cells (PBMCs), indicating proviral transcription and production of virions, i.e. an active reservoir of HIV. It is not known whether proviral copy number, HIV-1 transcription, and residual plasma viremia on ART are related.

Methods: We conducted a cross-sectional study of viremic patients off ART and of virologically suppressed (<50 cps/ml) patients on ART. PBMCs were tested for total cell-associated (CA) HIV-1 DNA and unspliced HIV-1 RNA using sensitive qPCR targeting 3′ pol. Plasma was tested for residual viremia by single copy assay targeting the same pol region. Unpaired t-test was used to compare viremic and patients on ART. Correlations between plasma viremia and cellular nucleic acids were assessed with Pearson's coefficient.

Results: 12 viremic patients and 23 patients on ART were studied. In patients on ART, median CA HIV-1 DNA was 310 copies/10^6 PBMCs (range: 45, 984) and median CA HIV-1 RNA was 59 copies/10^6 PBMCs (range: 1, 454), both were significantly lower than in viremic patients (median 565 [range: 48, 4680], $p = 0.033$; median 296 [range: 33, 19172], $p = 0.030$; for CA HIV-1 DNA and RNA, respectively). The 5-fold reduction in CA HIV-1 RNA on ART is small compared with the $> 4 \log_{10}$ difference in plasma viremia between these two groups (median 0.44 [range: 0.4, 26] vs. 10542 [range: 564, 474211] copies/mL on and off ART, respectively), indicating substantial persistence of HIV-1 transcription despite ART. A strong, positive correlation was detected between cell-associated HIV-1 DNA and unspliced RNA in both viremic (Pearson's $r = 0.974$; $p < 0.001$) and patients on ART ($r = 0.779$; $p < 0.001$). In viremic patients, the levels of plasma HIV-1 RNA also show strong, positive correlations with cell-associated HIV-1 DNA and RNA (Pearson's $r = 0.849$ and 0.843, respectively; $p < 0.001$). By contrast, in patients on ART, residual plasma viremia was not correlated with cell-associated HIV-1 DNA ($r = 0.06$; $p = 0.78$) or RNA ($r = -0.18$; $p = 0.39$).

Conclusions: This is the first study to show i) a strong, positive correlation between the number of HIV-infected cells and the level of cell-associated HIV-1 RNA in patients on ART, and ii) no correlation between cell-associated HIV-1 RNA and the levels of persistent viremia. These findings suggest that most of persistent HIV-1 transcription in patients on ART does not result in viremia.

380 Liver Macrophages and HIV-1 Persistence

Abraham J. Kandathil; Christine M. Durand; Jeffrey Quinn; Andrew Cameron; David L. Thomas; Ashwin Balagopal
Johns Hopkins School of Medicine, Baltimore, MD, US

Background: Cellular reservoirs of HIV-1 infection that persist despite combination antiretroviral therapy (cART) are impediments to a cure. The extent to which tissue resident macrophages (TRM) sustain infectious HIV-1 in patients on cART is unknown. We hypothesized that liver macrophages (LM),also known as Kupffer cells, comprising 80-90% of all TRM are a reservoir of HIV-1.

Methods: To test this hypothesis we used both *in vitro* and *in vivo* studies. Purified LM from 3 human donors were infected *in vitro* with an R5-tropic GFP reporter HIV-1 virus and supernatants were tested periodically for the presence of viral RNA. To assess their role *in vivo,* LM were purified from liver explants taken from HIV-1 infected persons with uncontrolled (n=1) and cART-suppressed viremia (n=2); viral outgrowth assays were performed on LM isolated from HIV-1 infected persons with cART-suppressed viremia to determine if purified LM contain infectious HIV-1. LM purity was confirmed using sensitive qPCR assays, and when required LM were incubated with a high-affinity T cell immunotoxin.

Results: LM were infected *in vitro* and were found to support infectious virus production for >170 days; LM supernatants were sufficient to propagate HIV-1 in reporter cells. Infectious virus was also recovered during and after *in vitro* exposure to cART for 24 days. Poly(A) HIV-1 RNA was detectable in LM supernatant from the individual with uncontrolled viremia (N7) 18 days after explantation, indicating virus release. Viral outgrowth assays demonstrated LM supernatants from HIV-1 infected persons (LT01 and LT02) with cART-suppressed viremia could transmit infection to reporter cells: LT01 and LT02 LM were maintained *ex vivo* for 36 and 95 days, respectively, before stimulation. After stimulation of LM, reporter cells were inoculated with LM supernatants for 36 (LT01) and 11 (LT02) days. Reporter cells were lysed and found to have proviral DNA (LT01: 2.4 cp/10^6 cells; LT02: 4.9 cp/10^6 cells). Reporter cells treated with LM supernatants from LT02 also released HIV-1 RNA at a level of 55 cp/100 μL on day 11 after inoculation. Notably, LT02 had a pre-cART plasma HIV-1 RNA level of 74 cp/mL **(Table).**

Liver Macrophages Harbor Infectious HIV-1 for Prolonged Durations and Despite cART.

	N1*	N2*	N3*	N4*	N5*	N6*	N7*	N8*	LT01^	LT02^
CD4+ T cell count (cells/μL)	-	4	-	9	379	860	53	67	607[a]	116[a]
HIV-1 RNA (cp/mL)	-	-	-	-	UD	UD	>500,000	136,896	UD[a]	UD[a]
cART	TDF/ddI/NFV	None	None	None	-	TDF/FTC/EFV	None	None	TDF/FTC/Ral	ABC/3TC/DTG
Pre-cART HIV-1 RNA (cp/mL)	-	-	-	-	-	-	-	-	-	74
Duration of cART (months)	-	-	-	-	-	-	-	-	137	8
Bulk Liver Proviral DNA (cp/10^6 cells) §	0.2	10.8	8.3	4.9	≤LOD	8.5	32.0	5.8	248.0	148.0
Isolated Liver Macrophages *ex vivo*	No	No	No	No	No	No	Yes	No	Yes	Yes
Ex vivo HIV-1 RNA (cp/100μL)	-	-	-	-	-	-	24.4	-	-	-
Viral Outgrowth Assay Proviral DNA (cp/10^6 cells)	-	-	-	-	-	-	ND	-	2.4	4.9
Viral Outgrowth Assay Released HIV-1 RNA	-	-	-	-	-	-	ND	-	-	55.4

Whole liver tissue was obtained from HIV-1 infected individuals at time of death (*) and during liver transplantation (^). After whole cell lysis, samples were tested for HIV-1 proviral DNA. Cell numbers were estimated using ERV3 DNA quantification from the same samples. The table indicates the latest available CD4+ T cell count, cART status, and plasma HIV-1 RNA before the recovery of liver tissues. a - Clinical laboratory values that were contemporaneous for LT. § - Proviral DNA was quantified using a qPCR assay that was adapted to detect tissue HIV. *liver samples were obtained from NDRI; HIV-1 RNA, cART status, HCV and HBV status are reported by NDRI. Data that was unavailable is indicated by "-". HIV-1 RNA, cART status, HCV and HBV status were available through clinical testing for LT01 and LT02. TDF – tenofovir disoproxil fumarate; ddI – didanosine; NFV – nelfinavir; FTC – emtricitabine; EFV – efavirenz; Ral – raltegravir; ABC – abacavir; 3TC – lamivudine; DTG – dolutegravir; UD – undetectable using a standard clinical assay. ND- not done.LOD- limit of detection

Conclusions: These data provide strong evidence that LM, the largest TRM population, release infectious HIV-1 after a prolonged duration; therefore, LM may represent an important reservoir of HIV infection and potential impediment to cure.

381 Large-Scale Analysis of HIV-1 Integration Sites in Untreated and Treated Patients

Stephanie Laufs[1]; **Diana Schenkwein**[1]; Neeltje Kootstra[2]; Frank A. Giordano[5]; Christoph Stephan[3]; Hans-Georg Kraeusslich[4]; Winfried Kern[6]; Susanne Usadel[6]; Manfred Schmidt[1]; Christof von Kalle[1]

[1]National Center for Tumor Diseases; German Cancer Research Center, Heidelberg, Germany; [2]Sanquin Research, Landsteiner Laboratory, and Center for Infectious Diseases and Immunity Amsterdam, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; [3]University Hospital Frankfurt, Frankfurt, Germany; [4]Department of Infectious Diseases, Virology, University Hospital Heidelberg, Heidelberg, Germany; [5]Heidelberg University, Heidelberg, Germany; [6]Division of Infectious Diseases, Department of Medicine, Albert-Ludwigs-University Center for Infectious Diseases & Travel Medicine, and IFB-Center for Chronic Immunodeficiency, University Hospital, Freiburg, Germany

Background: The HIV/AIDS pandemic remains an important threat to global health. Although cART (combination antiretroviral therapy) induces a rapid decline in plasma HIV-1 RNA, persistence of latent forms of HIV-1 displays the major hurdle on the way to eradicating the infection. Recent data indicate that at least a subset of patients harbor a sufficiently suppressed viral reservoir which is not able to fuel viral rebound upon therapy discontinuation. These so-called functionally cured patients provide new hope for an HIV cure by the elimination of replication-competent HIV-1 reservoirs.

Based on our experience from the analysis of more than 1 million lentivirus vector insertion sites (IS) we hypothesized that significant portions of inserted provirus in patients might be non-randomly distributed and/or clonally stable and/or within illegitimate, non-canonical LTR boundaries.

Methods: To study wtHIV IS in human patients, we determined genomic/proviral flanking regions in untreated (n=39) and cART treated (n=32, including amongst others an integrase inhibitor) patient cohorts using linear amplification-mediated PCR (LAM-PCR) in a longitudinal analysis. The clonal inventory of infected cells was obtained using next-generation sequencing combined with a novel double barcoding system in combination with innovative bioinformatic analysis. Integrome analysis was done to quantify chromosomal distribution of IS, illegitimate non-integrase mediated HIV-1 integration and clonal persistence indicative of virus-host genome interactions.

Results: Our data describe for the first time the existence of LTR micro-deletions in wtHIV infected CD4 positive patient cells. To generate the IS profile we identified more than 2500 integration sites from wtHIV-1 infected patient samples pre and post therapy and identified common IS.

To monitor longitudinal IS distribution, we performed high-throughput IS analysis at up to eight different time points up to 330 days after therapy. Identical IS were found at multiple time points proving the existence of a persisting reservoir of dividing infected cells in patients.

Conclusions: This finding is in line with recent reports where the authors postulate that the location of HIV ISs can promote the expansion and persistence on HIV infected cells (Maldarelli et al. 2014, Wagner et al. 2014). In addition our data proof LTR micro-deletions in wtHIV infected patient cells and focus on HIV integration in humans on a large cohort of treated and untreated patient samples.

382 Identical Sequence Expansions Are Predominantly Found in Effector Memory T Cells

Susanne von Stockenstrom[1]; Eunok Lee[2]; Lina Odevall[1]; Elizabeth Sinclair[3]; Hiroyu Hatano[3]; Peter Bacchetti[4]; Peter W. Hunt[3]; Steven G. Deeks[3]; Frederick M. Hecht[3]; Sarah E. Palmer[2]

[1]Karolinska Institutet, Stockholm, Sweden; [2]Westmead Millenium Institute and University of Sydney, Sydney, Australia; [3]Department of Medicine, University of California San Francisco, San Francisco, CA, US; [4]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, US

Background: The effects of cellular proliferation, differentiation and expansion on the maintenance and genetic composition of HIV-1 populations within specific T cells is uncertain.To address this issue, we examined the distribution of identical HIV-1 intracellular sequences from peripheral blood and lymph node tissue in order to define the role of cell proliferation as a cause of persistence.

Methods: Using single-proviral sequencing, we isolated intracellular HIV-1 genomes derived from defined subsets of CD4+ T cells (central (CM)-, transitional (TM)-, and effector (EM)-memory) from peripheral blood and lymph node tissue. Samples were collected from six subjects on long-term suppressive therapy (6-13 years) treated during chronic infection. Unique clonal populations of sequences were determined (for p6-RT) as $\geq$ 2 genetically identical sequences among all the viruses analyzed for each subject and we assessed the number of clonal populations found exclusively within a particular cell type. All clonal sequences were compared to pre-therapy plasma-derived single genomes.

Results: Phylogenetic analyses revealed that 30-60% of all HIV-1 sequences combined from the cells sorted from blood and lymph node tissue (n=93-243 per person) were clonal in nature, and that the mean number of clonal populations per subject was 14 (range 9 to 26). However, only a few (n=0-4) of these clonal sequences were found in pre-therapy plasma sequences. Clonal populations were more common in EM cells (61%) than other T cell subsets (25-49%). Across all subjects, the percentage of sequences in EM cells that were clonal sequences and found in no other cell types averaged 30%, whereas this average was <7% for CM or TM cells (both p=<0.0001 versus EM cells). The rates of such clonal populations associated with CM versus TM cells were not significantly different (p=0.21).

Conclusions: Sequences in EM cells were predominantly clonal. These clones were often not found in less differentiated cells. The source of these cells is not known, but may reflect infection and expansion directly of an infected EM population, or differentiation and expansion of infected progenitor cells in tissue. This suggests that different cellular mechanisms are contributing to the persistence of HIV within different memory T cell subsets and the size and distribution of the latent reservoir during suppressive therapy is likely to be shaped in part by proliferation and expansion of differentiated T cells.

383 Long-Term Effect of Temporary ART During Primary HIV Infection on the Viral Reservoir

Alexander Pasternak[1]; Jan Prins[2]; Ben Berkhout[1]

[1]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [2]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands

Background: Initiation of antiretroviral therapy (ART) during primary HIV-1 infection (PHI) has been proposed to limit the formation of viral reservoirs. However, it remains unknown whether temporary ART during PHI has a long-term effect on the viral reservoir during ART initiated subsequently at chronic HIV infection (CHI).

Methods: Levels of cell-associated (CA) HIV-1 unspliced RNA (usRNA) and total CA viral DNA (vDNA) were analyzed in 49 HIV-infected patients who had participated in a randomized controlled trial of 24 or 60 weeks of temporary ART versus no treatment during PHI (Primo-SHM study; PLoS Med 2012;9:e1001196). All 11 patients randomized to the no-treatment arm at PHI, and 19 of 38 patients randomized to receive ART at PHI, subsequently (re)started ART during CHI after a median period of 86 weeks without treatment. HIV nucleic acids were longitudinally quantified in PBMC at ART baseline time points and every 12 weeks thereafter up to week 60 of both PHI and CHI ART by seminested real-time PCR. We used mixed modeling to compare the variables between groups and Spearman tests for correlation analyses.

Results: Levels of usRNA and usRNA/vDNA ratios at PHI ART baseline strongly predicted the viral setpoint upon early therapy interruption (p=0.0001 and p=0.00004, respectively), and the slope of the CD4 count decline in the untreated period after interruption of early ART (p=0.009 and p=0.003). The predictive power of CA RNA for both viral setpoint and CD4 count decline was stronger than that of the plasma viremia. Levels of both usRNA (p=0.009) and vDNA (p=0.03) during PHI ART were significantly lower than levels of corresponding markers during CHI ART in patients who were not treated with early ART. However, no significant difference was found in the levels of any marker between the early and chronic therapy periods in the same patients, and strong correlations for all the markers between the two therapy periods were observed (usRNA: p=0.002; vDNA: p=0.0001, usRNA/vDNA: p=0.003). Finally, level of usRNA, measured during CHI ART, was significantly lower in patients who had been pre-treated during PHI than in patients who had not been pre-treated (p=0.018).

Conclusions: Level of CA HIV RNA at PHI strongly predicted the CD4 count decline, suggesting that the viral reservoir, established early after infection, influences the disease progression for years afterwards. We observed a long-term suppressive effect of temporary early ART on the viral reservoir during ART initiated subsequently at CHI.

THURSDAY, FEBRUARY 26, 2015

Session P-F3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Cellular Factors of Latency

384 Minor Contribution of Host-HIV Readthrough Transcripts to the Level of HIV-1 *gag* RNA

Alexander Pasternak[1]; Una O'Doherty[2]; Ben Berkhout[1]

[1]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [2]University of Pennsylvania, Philadelphia, PA, US

Background: Cell-associated (CA) HIV-1 unspliced RNA is an important marker of the viral reservoir and the response to antiretroviral therapy (ART). Recently it has been used in clinical trials as a measure of virus activation by latency-reversing agents. Primers specific for the HIV *gag* regions are frequently used in PCR-based assays that quantify unspliced RNA. However, because HIV-1 integrates within actively transcribed host genes, it has been suggested that some of the transcripts detected by the *gag*-specific assays may not represent genuine HIV RNA but rather chimeric host-HIV readthrough transcripts. To properly interpret the results of the *gag* assays, it is necessary to determine the relative contribution of such readthrough transcripts to the HIV *gag* RNA in ART-treated patients.

Methods: We developed a sensitive nested real-time PCR assay that amplifies the 5′ LTR-encoded U3 – packaging signal region (U3-Psi) of HIV-1. This assay specifically measures host-HIV readthrough transcripts but does not detect genuine HIV-1 unspliced RNA (Fig. 1). Total DNA and total RNA were isolated from PBMC samples of 48 ART-treated patients whose plasma viremia had been undetectable (<40 copies/ml) for ≥1 year prior to the study. CA HIV-1 DNA and RNA were separately quantified in these samples using both the U3-Psi assay and the seminested real-time PCR assay specific for the HIV-1 *gag* region. The sensitivity of both assays is 4 copies/reaction. The same inputs of DNA or RNA were used for both assays.

Results: As expected, both U3-Psi and *gag* assays detected HIV-1 DNA in >90% of the patients (44/48 and 46/48, respectively) with no significant quantitative bias between the assays, demonstrating the functionality of the U3-Psi assay. HIV-1 *gag* RNA was detected in 44/48 of these patients (92%) with the median copy number of 590 (interquartile range, 217-1194) copies/μg total RNA. However, the detectability of readthrough RNA was only 40% (19/48 patients). In the 19 patients where the readthrough RNA was detected, its copy number was 49 (41-122) copies/μg total RNA, representing only 8.3% (2.4%-11.2%) of the HIV-1 *gag* RNA. Notably, the real readthrough/*gag* RNA ratio is much lower, as patients with undetectable readthrough RNA (60% of all patients) were excluded from this calculation.

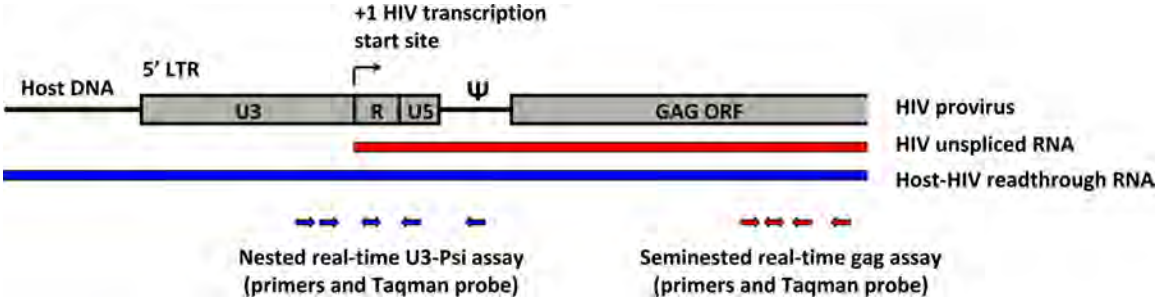


Figure 1. Schematic representation of real-time PCR assays for the detection of readthrough and *gag* RNA. LTR, long terminal repeat; ORF, open reading frame; Ψ, HIV packaging signal (Psi).

Conclusions: We observed only a minor contribution of host-HIV-1 readthrough transcripts to the level of HIV-1 *gag* RNA. The vast majority of HIV-1 *gag* RNA transcripts in ART-treated patients represent genuine HIV-1 unspliced RNA.

385 MicroRNA-155 Reinforces HIV Latency by Downregulating the TRIM32 Viral Activator

Debbie S. Ruelas[2]; Jonathan Chan[2]; Eugene Oh[1]; Amy Heidersbach[2]; Andrew Hebbeler[2]; Leonard Chavez[2]; Eric Verdin[2]; Warner C. Greene[2]
[1]*University of California San Francisco (UCSF), San Francisco, CA, US;* [2]*University of California Berkeley, Berkeley, CA, US*

Background: Achieving a cure for HIV will require both the complete suppression of active viral replication and the clearance of the transcriptionally silent proviral latent reservoir. Current drug treatments effectively target the active virus but leave the latent reservoir intact. We describe a cellular pathway involving miR-155 and one of its many cellular targets, TRIM32, that appears to promote a return to latency in reservoir cells transiently producing virus.

Methods: We first assessed whether miRNAs play a role in maintenance of viral latency by separately knocking down the expression of two of the major enzymes involved in miRNA biogenesis, DGCR8 and Dicer, in J-Lat 5A8 cells. We next used miRNA TLDA analysis to identify specific miRNAs that alter the level of reactivation following stimulation. We focused on miR-155 because its reintroduction into Dicer-deficient cells was able to rescue the level of latent reactivation in J-Lat 5A8 cells to the greatest extent, suggesting that it plays a prominent role in reinforcing HIV latency. We confirmed TRIM32 as a novel target of miR-155 using luciferase binding assays. An IkB kinase (IKK) kinase assay revealed that TRIM32 acts downstream of the IKKs. Finally, our i*n vitro* ubiquitination assays demonstrate that TRIM32 is able to directly ubiquitinate IκBα.

Results: MiR-155, which is expressed at high levels in activated cells, impairs the expression of TRIM32, which normally serves as an HIV-activating agent. TRIM32 activates latent HIV by stimulating nuclear translocation of NF-κB. However, our studies reveal that TRIM32 activates NF-κB in a novel manner involving direct ubiquitination of IκBα. Specifically, TRIM32 induction of NF-κB proceeds independently of IKK activation within signalosomes.

Conclusions: Our studies of the potential role of microRNAs in the regulation of HIV latency have led to the identification of miR-155 and its inhibition of TRIM32 activation of NF-κB as events that promote the reestablishment of HIV latency in reservoir cells undergoing transient viral production.

386 Select Host Restriction Factors Are Associated With HIV Persistence During Therapy

Mohamed Abdel-Mohsen[1]; Leonard Chavez[1]; Charlene Wang[1]; Matt Strain[2]; Xutao Deng[1]; Christopher D. Pilcher[3]; Teri Liegler[3]; Douglas D. Richman[2]; Steven Deeks[3]; Satish Pillai[1]
[1]*Blood Systems Research Institute, San Francisco, CA, US;* [2]*University of California San Diego, La Jolla, CA, US;* [3]*University of California San Francisco, San Francisco, CA, US*

Background: Although antiretroviral therapy (ART) results in sustained inhibition of HIV replication, the virus may continue to replicate at low levels. Moreover, ART has no effect on cells harboring integrated and silenced DNA ("latent reservoir"). A number of retroviral restriction factors have been identified which directly inhibit viral replication *in vitro*. However, the potential impact of these cell-intrinsic immune factors on viral persistence during ART is unknown. We investigated the relevance of a comprehensive panel of anti-HIV-1 host restriction factors to multiple virologic and immunologic measures of viral persistence in a cohort of 72 HIV-infected, ART-suppressed individuals.

Methods: We measured the expression of 42 anti-HIV-1 host restriction factors, levels of cell-associated HIV-1 RNA, total *pol* and 2-LTR circle HIV-1 DNA, and immunophenotypes of CD4+ T cells from 72 HIV-1-infected subjects on suppressive ART (23 subjects initiated ART <6 months post-infection, and 49 subjects initiated >1 year post-infection). Data were analyzed using non-parametric tests.

Results: The enhanced expression of three host restriction factors (p21, schlafen 11, and PAF1) was strongly associated with reduced CD4+ T cell-associated HIV RNA during ART ($p<0.001$). In contrast to previously published data on ART-untreated individuals, the expression of several restriction factors during ART exhibited negative correlations with frequencies of CD4+ T cells expressing markers of T cell activation and exhaustion (CD38, HLA-DR, PD-1) ($p<0.01$). Cell-intrinsic immune responses were significantly enhanced in subjects who initiated ART during early versus chronic infection ($p=0.02$).

Conclusions: A few select intrinsic immune responses may modulate HIV persistence during suppressive ART, and therefore may be manipulated to both enhance the efficacy of ART and/or reverse latency *in vivo*. For example, inhibition of p21, which is known to suppress HIV transcription post-integration, may promote viral reactivation in the setting of the shock and kill eradication framework. Our data also suggest that ART perturbs the regulatory relationship between CD4+ T cell activation and restriction factor expression, which is pertinent to latency reversal agents that activate infected cells. The enhanced intrinsic immune response observed when ART is initiated early provides another possible justification for early administration of ART, and may contribute to the smaller reservoir size noted when ART is initiated early.

387 Selectively Eliminating HIV Latently Infected Cells Without Viral Reactivation

Grant R. Campbell; Rachel S. Bruckman; Yen-Lin Chu; Stephen A. Spector
University of California San Diego, La Jolla, CA, US

Background: Efforts to disrupt the establishment and maintenance of the latent reservoir have focused on the "shock-and-kill" therapeutic approach to reverse HIV latency from $CD4^+$ T cells with subsequent killing of the infected cells. The X-linked inhibitor of apoptosis protein (XIAP) is up regulated in latently infected cell lines. In this study, we

investigated whether this molecular signature existed in primary latently-infected resting central memory CD4+ T cells and whether this could be used to selectively target and kill latent HIV harboring cells.

Methods: CCL19-treated naïve CD4+ T cells isolated from HIV-uninfected donors were infected with HIV then expanded in the presence of IL2 for 12 d. Memory CD4+ T cells were then isolated and cultured in the presence of IL7 for a further 20 d then analyzed by flow cytometry. HIV integration was analyzed by Alu-LTR qPCR. Expression of XIAP was assessed using Western blotting. HIV p24 antigen was quantified by ELISA. Long-lived, resting memory CD4+ T cells were then treated with the XIAP antagonist GDC-0152, the SMAC mimetic antagonist birinapant or the inhibitor of XIAP embelin. Apoptosis was assessed using annexin-V combined with propidium iodide staining as well as by Western blotting for PARP and caspase 3 cleavage. Data were analyzed using the Student's *t* test.

Results: After the 32 d infection, CD4+ T cells displayed a resting central memory CD4+ T cell phenotype (CD45R0+ CD62L+ CCR7+ CD25- Ki-67-). Alu-LTR qPCR and p24 ELISA demonstrated that these cells contained the equivalent of 1 copy of integrated HIV DNA in the absence of viral release into the culture supernatant. Moreover, XIAP expression was significantly increased compared with uninfected cells ($P < 0.05$). Targeting XIAP with birinapant, GDC-0152, and embelin resulted in a significant dose-dependent increase in the number of latently infected resting central memory CD4+ T cells undergoing apoptosis which was not observed in mock-infected cells. Moreover, we did not observe an increase in p24 antigen expression.

Conclusions: We have identified XIAP as a molecular signature of latently infected primary long-lived, resting central memory CD4+ T cells. Moreover, these cells are more sensitive to XIAP-agonist-induced apoptosis than uninfected cells. Therefore, by targeting XIAP with selective inhibitors and antagonists we have developed a novel approach that selectively eliminates latently-infected cells that does not require reactivation of HIV gene expression.

388 PD1 Identifies Latently HIV-Infected Nonproliferating and Proliferating CD4+ T Cells

Renee M. van der Sluis[1]; Nitasha A. Kumar[1]; Vanessa A. Evans[1]; Rafick P. Sekaly[2]; Remi Fromentin[2]; Nicolas Chomont[2]; Paul U. Cameron[1]; Sharon R. Lewin[1]

[1]*Doherty Institute, Melbourne University, Melbourne, Australia;* [2]*VGTI-Vaccine and Gene Therapy Institute Florida, Port St. Lucie, FL, US*

Background: CD4+ T-cells from HIV-infected individuals on antiretroviral therapy (ART) expressing the Immune Checkpoint (IC) marker of T-cell activation PD1, are preferentially infected [Chomont Nat Med 2009]. Characterizing the role of PD1 and other IC in HIV persistence during ART may identify new potential targets for eliminating latently infected T cells. Using an *in vitro* model of latency, we aimed to define the mechanism of how PD1 and other IC contribute to the establishment and maintenance of latent infection of both proliferating and non-proliferating T-cells.

Methods: Resting CD4+ T-cells, isolated from blood of HIV-negative individuals, labelled with the proliferation dye eFluor670, were cultured alone, with autologous blood myeloid dendritic cells (mDC) or monocytes for 24h with staphyloccocal enterotoxin B (SEB). Cells were infected with CCR5-tropic eGFP-reporter virus. Expression of IC ligands including PDL1/PDL2 (ligands for PD1), CD80/CD86 (ligand for CTLA4), Galectin 9 (possible ligand for Tim3) and herpes virus entry mediator; HVEM (ligand for B and T cell attenuator (BTLA)) on mDC and monocytes were measured at baseline and 24h post infection. Non-productively-infected, non-proliferating (eGFP-eFluor670^{hi}) and proliferating (eGFP-eFluor670^{lo}) T-cells were sorted by flow cytometry day 5 post infection and further sorted on the basis of IC expression, including PD1, Tim3, CTLA4, BTLA, TIGIT or LAG3. Inducible latent infection was quantified by measuring eGFP expression in sorted subsets after αCD3/CD28+IL-7+IL-2 activation and integrase inhibitor L8.

Results: Ligands for all IC were expressed, albeit at differing levels, on mDC and monocytes 24h post T-cell co-culture and HIV infection. Post integration latency in **non-proliferating CD4+ T-cells** was significantly enriched in cells positive for PD1 (mean fold change in eGFP expression compared to PD1 negative (MFC) =39, p=0.02, n=5), Tim3 (MFC=3.4, p=0.04, n=6), CTLA-4 (MFC=4.4, p=0.01, n=4) or BTLA (MFC=4.2, p=0.004, n=6) but not TIGIT (MFC=2.9, p=0.24, n=5) or LAG3 (MFC=2.9, p=0.67, n=3). Post integration latency in **proliferating T-cells** was significantly enriched in cells expressing PD1 (MFC=2.8, p=0.04, n=5) but not other IC.

Conclusions: This *in vitro* model of HIV latency shows PD1 to be preferentially expressed on both non-proliferating and proliferating latently infected T-cells. Interventions that alter expression or function of PD1 should be explored to eliminate latency.

389LB 2B4+PD1+ Naïve and Memory CD4+ T Cells Are Associated With Residual Viremia on ART

Cynitha Klamar; Feiyu Hong; John Bui; Anthony R. Cillo; Arcadio Agudelo-Hernandez; Deborah A. McMahon; Charles R. Rinaldo; John W. Mellors; **Bernard J. Macatangay**

University of Pittsburgh, Pittsburgh, PA, US

Background: CD4+ T cell expression of inhibitory receptors (IRs) has been reported to be a marker of latently HIV-infected cells. We determined whether co-expression of various IRs on naïve (T_N) and memory (T_M) CD4+ T cells is associated with persistent HIV-1 expression in patients on effective ART.

Methods: Expression of PD1, CTLA4, TIM3, 2B4, CD160, and LAG3, in CD4+ T cells from patients on suppressive ART was determined using flow cytometry. Boolean gating using Flowjo was done to evaluate 57 different combinations of inhibitory receptors in naïve (CD45RA+ CCR7+), central memory (T_{CM}; CD45RA-CCR7+), and effector memory (T_{EM}; CD45RA-CCR7-), CD4+ T cells. PBMC and plasma were tested for cell-associated HIV DNA (CA-DNA) and RNA (CA-RNA) and residual viremia using qPCR targeting 3' pol. Correlation between markers was assessed using Spearman's rho.

Results: PBMC were analyzed from 30 patients on suppressive ART (<50 copes/ml) for a median of 7.4 years. Of the T_N and T_M expressing a single IR, frequencies were highest for those expressing TIM3 alone (mean: T_N=42.6%, T_M=23.9%) followed by PD1 and 2B4. Single-expression of the other 3 IRs was seen in <0.5% of the cells. Correlations between the frequencies of single-expression of TIM3, PD1, or 2B4 on T_N, T_{CM}, and T_{EM} and residual viremia were modest (with R values<0.45; p=0.01-0.04). No correlations were seen with CA-DNA or RNA. Evaluation of multiple IR co-expression (i.e. 2-6 IRs expressed) revealed that the combinations PD1/TIM3/2B4+, PD1/2B4+, PD1/TIM3+, PD1/2B4+ had the highest frequencies (mean: T_N=3.9% T_{CM}=6.1% T_{EM}=7.9%), whereas the other 53 IR combinations had frequencies <0.1%. Although PD1/TIM3+ cells had the highest frequencies (T_N=10.7% T_{CM}=19.1% T_{EM}=20.1%), PD1/TIM3 expression only modestly correlated with residual viremia for T_N only (R=0.42; p=0.02), and with CA-DNA in T_{EM} (R=0.40; p=0.03). By contrast, highly significant correlations were observed between residual viremia and PD1/2B4+ T_N (R=0.59; p<0.001) and PD1/2B4+T_{CM} (R=0.57, p=0.001), but not with CA-RNA or -DNA.

Conclusions: In patients on suppressive ART, a substantial fraction of naïve and memory CD4+ T cells co-express different combinations of PD1, 2B4, and TIM3. The specific combination of PD1 and 2B4 co-expression on naïve and central memory is strongly associated with the level of residual viremia on ART, suggesting that targeting more than one IR could be needed to maximize effects of HIV-1 persistence.

390 Nascent LTR-Driven Transcription Can Lead to Translation of HIV Proteins in Resting CD4+ T Cells

Laura DeMaster[1]; Alexander Pasternak[2]; Una O'Doherty[1]

[1]*University of Pennsylvania, Philadelphia, PA, US;* [2]*Academic Medical Center University of Amsterdam, Amsterdam, Netherlands*

Background: We have previously described a model of direct infection of resting CD4+ T cells and contrasted it with models of activated CD4+ T cell infection. We found that infected resting CD4 cells express low levels of viral protein without releasing infectious virus, raising the possibility that reservoirs may express HIV proteins in vivo and be visible

to the immune system. Unspliced RNA (usRNA) encoding gag was the predominant HIV RNA form detected in infected resting cells. We designed experiments to ask if nascent transcription occurs in resting CD4+ T cells or if the Gag signal detected is due to an artifact such as read-through transcription or incoming virus.

Methods: To address the contribution of incoming virus to Gag signal, we first sorted Gag+ and Gag-negative cells from cultures infected in vitro and measured levels of HIV DNA in both populations, similar to an approach we used in vivo. RT-PCR and FACS analysis were used to determine whether other viral proteins (made from spliced RNA forms) were present in cells infected in vitro and in CD4+ T cells from ART patients. In addition, given that tat/rev is present at very low levels in vivo in patients on ART, we asked if tat/rev is required for LTR driven expression.

Results: We found that Gag+ cells were strongly (more than 100-fold) enriched for HIV DNA compared to Gag-negative cells in infected cultures. In addition to spliced HIV RNA forms, further evidence of nascent transcription included direct and indirect evidence of new synthesis of multiple HIV proteins by FACS. Read-through transcripts were detectable but present at low levels compared to gag RNA in both cells infected in vitro and in CD4 cells from ART patients. Stimuli such as IL-7 and Romidepsin preferentially induced gag usRNA over read-through transcripts. In contrast, SAHA induced both read-through and gag usRNA transcription two-fold. Notably, we show that low-level protein expression can occur in the absence of tat/rev using a viral vector with a deletion of tat/rev gene expression.

Conclusions: Nascent LTR transcription occurs in HIV-infected resting CD4+ T cells. In vitro and in vivo data suggest that Gag is the predominant transcript (usRNA) and protein expressed in HIV infected individuals on ART. The relative contributions of replication competent and defective proviruses to viral protein expression in vivo remain undefined.

WEDNESDAY, FEBRUARY 25, 2015

Session P-F4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Dynamics of Latency and Reactivation

391 Influenza Vaccination Increases HIV-1 Transcription During Antiretroviral Therapy

Christina C. Yek[1]; Sara Gianella[1]; Montserrat Plana[2]; Pedro Castro[2]; Felipe Garcia[2]; Marta Massanella[1]; David M. Smith[1]

[1]*University of California San Diego, San Diego, CA, US;* [2]*University of Barcelona, Barcelona, Spain*

Background: Curative strategies using stimulators such as histone deacetylase inhibitors, disulfiram and IL-7 to reactivate HIV have thus far demonstrated only modest activity. In contrast, transient increases in viremia after administration of standard vaccines have been observed even during antiretroviral therapy (ART). In this study we investigate whether routine influenza vaccination can reactivate HIV.

Methods: Eleven HIV-infected individuals on suppressive ART (<50 copies/ml) were selected from the intervention arm of a randomized trial that studied the effects of a vaccination schedule on viral rebound after structured treatment interruption (NCT00329251). Blood samples were obtained at baseline and 1 month after influenza vaccination. DNA and RNA were extracted from cryopreserved peripheral blood mononuclear cells using a Qiagen AllPrep DNA/RNA Mini Kit. Cell-assoiated HIV DNA and RNA transcripts were quantified by droplet digital PCR using primers for *gag* and 2-LTR (for HIV DNA), unspliced *gag* RNA (HIV usRNA), multispliced *tat-rev* RNA (HIV msRNA), polyA and RPP30 (cellular marker for normalization). Values were adjusted for percentage of CD4 T cells as measured by flow cytometry.

Results: Nine of 11 subjects showed an increase in HIV usRNA after influenza vaccination despite undetectable viral loads throughout. Median HIV usRNA levels pre- and post-vaccination were 28.7 [4.2-56.4] and 91.0 [43.2-173.1] copies/10^6 CD4 T cells, respectively (p=0.049). Mean increase in HIV usRNA after vaccination ranged from 0 to 49-fold (mean 10.6). No significant changes were observed in HIV msRNA (p=0.25), polyA (p=0.91), total HIV DNA (p=0.15), or 2-LTR circle copies (p=0.74).

Conclusions: This study demonstrated a clear increase in cell-associated HIV usRNA 1 month after influenza vaccination, consistent with antigenic stimulation of the HIV reservoir during suppressive ART. The mean 10.6-fold increase in HIV usRNA is comparable to or better than that seen with administration of Vorinostat. Total HIV DNA and 2-LTR circles did not change, suggesting reactivation of replication-incompetent virus and/or ART-mediated suppression of viral propagation. Although we do not propose that standard vaccinations will cure HIV, these findings suggest that a component of immune stimulation could be considered in the development of eradication strategies.

392 Defective HIV-1 Proviruses Can Be Transcribed Upon Activation

Ya-Chi Ho; Ross Pollack; Patrick Yong; Robert F. Siliciano

Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: HIV-1 persists in the latent reservoir, primarily resting memory CD4+ T cells, as integrated proviruses. The majority of these proviruses are defective, containing large internal deletions or APOBEC-mediated G-to-A hypermutations. However, we previously found that even if the HIV-1 genome contains lethal mutations, the LTR promoter may remain intact, indicating that HIV-1 RNA may still be transcribed. The transcription of HIV-1 RNAs from defective proviruses may complicate the measurement of the size of the latent reservoir using latency reversing agents during the shock-and-kill strategy, as measurement of the defective proviral RNA does not indicate the reactivation of the clinically significant replication-competent proviruses. Further, whether the cells harboring defective proviruses would expand upon reactivation, or would be eliminated by cytolytic T cells (CTLs), remains unknown.

Methods: Resting CD4+ T cells from aviremic patients under suppressive antiretroviral therapy are activated with CD3/CD28 costimulation under enfurvitide to prevent new rounds of in vitro infection. Autologous CTLs were stimulated with Group M Consensus Gag peptide mixture and IL-2. To examine whether cells containing intact or defective HIV-1 can be eliminated by CTLs, we co-cultured pre-stimulated autologous CTLs with activated CD4+ T cells. Cell-associated RNA and proviral DNA from cells which are resting, activated, and CTL co-cultured was subjected to quantitative PCR and deep-sequencing of the Gag region to examine the start codon of Gag and two tryptophan residues, which are hotspots APOBEC-mediated hypermutations. CTLs were removed by magnetic bead depletion from the CTL-CD4 coculture before qPCR for normalization to CD4 cell count.

Results: We found a significant proportion of the HIV-1 RNA in activated patient CD4+ T cells contains lethal mutations. The amount of defective proviruses increased over the course of activation, indicating expansion of cells containing defective proviruses upon stimulation. The percentage of defective proviruses increased, implying the effect of viral cytopathic effects by reactivated intact proviruses. The amount of HIV-1 proviruses, both intact and defective, decreased after addition of CTLs in some patients, indicating possible elimination by CTLs.

Conclusions: Defective HIV-1 proviruses may be transcribed during latency reversal. Cells containing defective HIV-1 proviruses may expand under T cell activation.

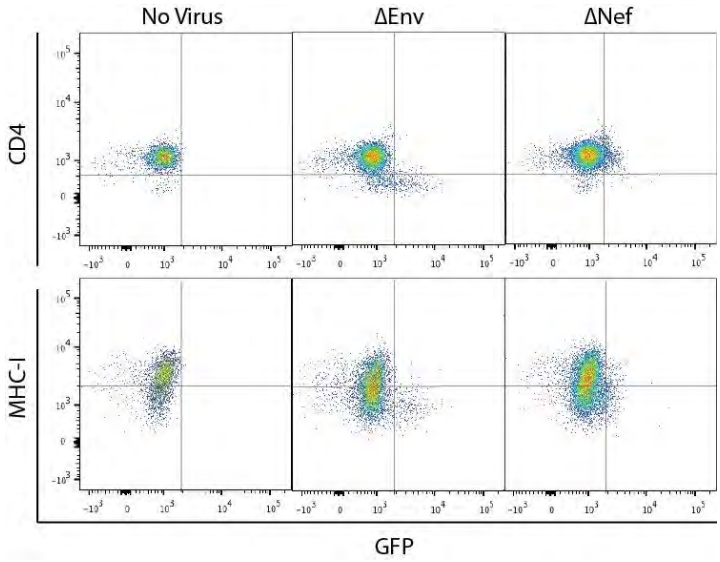
393 Kinetics of HIV-1 Gene Expression Following Reactivation in a Primary Cell Model of Latency

Victoria Walker-Sperling; Joel Blankson
Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: CD4+ T cells latently infected with HIV-1 pose a significant barrier to eradication. Proposed "shock and kill" strategies involve using small molecules to reactivate latent HIV-1 without causing the massive toxicity associated with non-specific T cell activation. Previous work suggests that the CD8+ T cell response must be augmented in patients for this strategy to work. While HAART will prevent new rounds of infection when latent virus is reactivated, the immune response must be capable of eliminating the few HIV-infected cells that will inevitably be left when treatment ceases. In order for CD8+ T cells to prevent new rounds of infection following reversal of latency, they must kill infected CD4+ T cells prior to the completion of the viral life cycle. Thus, we examined the kinetics of HIV-1 gene expression in a primary cell model of latency in the context of reactivation to determine the optimal time frame for CD8+ T cell mediated killing.

Methods: In order to establish a primary cell model of latency, resting CD4+ T cells were isolated from peripheral blood mononuclear cells (PBMCs) and nucleofected with HIV-1_{NL4-3} reporter-virus DNA that either had GFP replacing *env* or *nef*. The cells were then stimulated with anti-CD3/CD28 Dynabeads. Autologous Gag peptide stimulated CD8+ T cells from HAART-suppressed chronic progressors (CP) and elite suppressors (ES) were co-cultured with the resting CD4 T cells to assess susceptibility to killing. FACS analysis was performed at 6, 12, 18, 24, 36, and 42 hours.

Results: Env, Gag, and Nef were produced as early as 6 hours post-stimulation. Downregulation of surface MHC-I and CD4 molecules was seen as early as 6 hours post-stimulation. The MFI of these markers on infected cells was 30% less than uninfected cells in the same well, and CD4 was downregulated by 40-50%. In ES and CP, CD8+ T cell-mediated elimination of infected cells was measurable as early as 18 hours post-stimulation.



Downregulation of CD4 and MHC-I in HIV-1 Reactivation. For the virus lacking Nef (ΔNef), HIV-1+ cells display far less downregulation of CD4 and MHC-I than those that retain it (ΔEnv). GFP indicates HIV+ cells and is expressed instead of Env or Nef. Representative graphs from 12 hours post-stimulation.

Conclusions: Both early (Nef) and late (Env and Gag) proteins were produced by six-hours after activation of target CD4+ T cells, and downregulation of CD4 and MHC-I has already begun by that point in time. Despite the downregulation of MHC-I, stimulated CD8+ T cells were capable of modest elimination of CD4+ T cells producing viral proteins beginning as early as 18 hours post-stimulation of the target cells. The results suggest that it may be possible to eliminate recently reactivated, latently-infected cells before new rounds of viral replication occur.

394 Variable HIV Replication Competency Following Latency Disruption in CD4+ T Cells

Jason M. Hataye; Joseph Casazza; David Ambrozak; Eli Boritz; Takuya Yamamoto; Daniel Douek; Richard A. Koup
National Institute of Allergy and Infectious Diseases, Bethesda, MD, US

Background: The size of the latent reservoir in a patient with ART induced HIV suppression can be estimated by viral outgrowth in a limiting dilution culture of CD4+ T cells under activating conditions with exogenous cells and IL-2. A culture well containing HIV is typically detected with p24 ELISA, but recently HIV RNA RT-PCR has been shown to be more sensitive. This allowed us to determine the proportion of cells producing viral RNA that resulted in replication competent virus.

Methods: Resting memory CD4+ T cells from 9 virally suppressed patients were stimulated with beads coated with antibodies against CD2, CD3, and CD28, and plated in limiting dilution in two conditions: 1) 100,000 MOLT-4/CCR5 cells per well and IL-2 were added on day 1 to facilitate viral outgrowth, or 2) the reverse-transcriptase inhibitor efavirenz (EFV) was present immediately on day 0 to suppress viral replication, with no exogenous cells or IL-2 added. Culture media was collected and replaced every 4 days, and the viral RNA was isolated using a paramagnetic nanoparticle based method. Real time HIV *gag* RT-PCR was performed and the frequency of HIV RNA producing cells was calculated using the R package for Extreme Limiting Dilution Analysis.

Results: The frequency of HIV RNA producing cells following latency disruption was strongly correlated under viral outgrowth vs. viral suppression conditions. In most positive wells under viral suppression, viral RNA was detectable by day 4; some were followed by an increase while others decreased. In some outgrowth wells, the amount of HIV RNA on days 8 and 12 greatly exceeded that in comparable wells in the suppression assay. Culture supernatant from each positive outgrowth well was used to infect new cultures of activated but uninfected allogeneic CD4+ T cells. 33 of the 78 (42%) original positive outgrowth wells contained culture-confirmed replication competent virus, with significant well-to-well and patient-to-patient variability in the amount of virus produced.

Conclusions: While HIV *gag* RNA RT-PCR with a concentrated viral suppression culture was as sensitive for quantifying the frequency of HIV RNA producing cells as a viral outgrowth assay, much HIV RNA recovered in the outgrowth wells, including many wells that had increasing amounts of viral RNA over time, did not represent replication-competent virus.

395 Latent HIV-1 Reactivation and Lysosomal Destabilization Synergize to Host Cell Death

Metodi Stankov[1]; Christina Suhr[1]; Hazel Lin[1]; Diana Panayotova-Dimitrova[2]; Christine Goffinet[1]; Georg Behrens[1]
[1]Hannover Medical School, Hannover, Germany; [2]Mannheim Clinic of University of Heidelberg, Mannheim, Germany

Background: Modern strategies for purging the latent HIV-1 reservoir use pharmacological reactivation followed by elimination of cells that reactivated viral latency either by the virus or/and patient's immune system 'shock and kill'. Unfortunately, most of the current approaches demonstrated only partial reactivation and limited reduction of the reservoir. We aimed to develop a pharmacological strategy targeting cellular pro-survival mechanisms in order sensitize and eliminate host cells with even low or incomplete levels of HIV-1 reactivation.

Methods: We used in vitro models of HIV latency (J-lat full length clones, ACH2 and U1) and the latency-reversing agent panobinostat (Pan). We targeted the pro-survival pathway of autophagy and lysosomal integrity by the lysosome-destabilizing agents (LDA) chloroquine (CQ) or mefloquin (Mef). Autophagy and lysosomal pathways were monitored using flow cytometry, fluorescent microscopy and western blotting. Latent HIV-1 reactivation was confirmed through HIV-1-GFP expression, intracellular p24 abundance, and secretion

Results: Our results confirmed that CQ and Mef suppress autophagic flux and destabilize lysosomal membrane. Pan mediated reactivation led to specific cell death, which closely correlated to the levels of reactivation (R^2=0.8821; p=0.0178). At Pan concentrations associated with HIV-1 reactivation, but only little host cell death, co-treatment with CQ increased the death rate about four fold (Control 1.71%; Pano 17.4%; CQ 10% and Pano+CQ 63.2% p<0.0001). These synergistic and selective effects were further enhanced and were more rapid when we combined lysosomal disruption by Mef with boosted lysosomal activity by partial nutrient reduction (Control 9.2%; Pano 23.6%; Mef 8.8%, RPMI 13.3 and Pano+Mef+RPMI 74.7% p<0.0001).

Conclusions: We conclude that interference with the pro-survival pathway of autophagy at the level of lysosomal stability efficiently supports host cell death upon incomplete HIV-1 reactivation. These in vitro results suggest that combined pharmacological intervention may assist to eradicate latently HIV-1 infected cells.

396 Noninduced Proviral Genome Characterization in Perinatal HIV Infection

Kaitlin Rainwater-Lovett[1]; Carrie Ziemniak[1]; Douglas Watson[2]; Katherine Luzuriaga[3]; Priyanka Uprety[4]; Yahui Chen[1]; Ya-Chi Ho[1]; Deborah Persaud[1]
[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]University of Maryland, Baltimore, MD, US; [3]University of Massachusetts Medical School, Worcester, MA, US; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: The latent HIV reservoir was recently estimated as 60-times larger than previously thought due to replication-competent, non-induced proviral genomes (NIPG), creating a major impediment for cure. The frequency of circulating cells harboring proviral DNA approaches the limit of detection of ultrasensitive droplet digital PCR (ddPCR) in perinatally-infected individuals who initiated antiretroviral therapy (ART) before 6 months of age, suggesting early ART affects reservoir establishment. The extent to which NIPG contribute to HIV persistence in early treated perinatal infection is unknown.

Methods: P24-negative culture wells each containing one million resting CD4+ T cells from 21 perinatally-infected individuals aged 4-21 years who were virologically-suppressed by 6 months of age and for a median of 13 years (IQR: 10.5, 16) were screened for HIV *rt* or *gag* by nested PCR. The *gag* gene was sequenced from near full-length HIV amplicons at a clonal level as described by Ho et al. Total HIV DNA concentrations were quantified with ddPCR. Values below the limit of detection were set to the limit of detection.

Results: The median proviral burden was 15.2 copies HIV DNA/million resting CD4+ T cells (IQR: 4.8, 33.2). Of 426 million cultured resting CD4+ T cells, 9 wells yielded inducible provirus from 5 individuals (24%), resulting in a median of 0.067 infectious units per million cells. Of the remaining 389 p24-negative culture wells, 81 wells (19%) from 16 individuals yielded 281 NIPG *gag* sequences; of which, 188 (67%) were intact, 62 (22%) were hypermutated, and 31 (11%) contained major deletions. Individuals with induced provirus had 25% (95% CI: 13%, 38%) more intact and 8% (95% CI: 6%, 27%) fewer hypermutated *gag* sequences among their NIPG than those without induced provirus (p=0.001 and 0.021). The proportion of *gag* sequences with deletions did not differ between those with (4%) and without (12%) induced provirus (p=0.160). The proportion of 41 near-full length sequences obtained from the 188 NIPG with intact gag sequences with major deletions did not differ between those with (70%) and without (65%) induced provirus (p=1.00).

Conclusions: Early treated, perinatally-infected individuals readily harbor NIPG. Individuals with non-inducible provirus had few intact and many hypermutated NIPG, suggesting NIPG analysis in combination with quantitative co-culture are important measures for identifying perinatally-infected children who may benefit from immunotherapeutic approaches.

397 Multiple Rounds of T-Cell Activation Induce Additional HIV-1 From the Latent Reservoir

Nina N. Hosmane; Adam A. Capoferri; Robert F. Siliciano
Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: HIV-1 has the ability to establish latency within resting memory CD4+ T cells, generating a major barrier to eradication. The current gold standard assay to measure the size of the reservoir is the viral outgrowth assay (VOA), which uses a lectin, PHA, to induce global activation of resting CD4+ T cells from patients on antiretroviral therapy (ART). Previous studies have shown that the size of the latent reservoir may be 60-fold larger than originally estimated due to the presence of proviruses that are genetically intact, but are not detected in the VOA following a single round of T cell activation. We hypothesize that multiple rounds of T cells activation will induce additional outgrowth of viruses from the latent reservoir, thus providing a better indication of the true size of the reservoir.

Methods: Resting CD4+ T cells are isolated from patients on ART and plated at 200,000 cells per well in a VOA. After 8 days of culture with PHA, half of the volume from each initial well is split into new wells for a second round of PHA stimulation, performed in the same manner as the first round. After another 8 days, half the volume from these wells is split again into replicate wells, and so forth for a total of 4 stimulations. Viral outgrowth is detected 21 days following each respective round of PHA stimulation by both a p24 ELISA and a qPCR that detects full-length HIV-1 mRNA.

Results: Our results demonstrate that additional viral outgrowth is observed after additional rounds of activation. In some patients, most of the virus is induced in the first and second rounds of activation, while in other patients, each round induces additional latently infected cells to produce virus. The data demonstrates that one round of maximum T cell activation is not sufficient to induce all proviruses that are capable of producing replication-competent virus.

Conclusions: We conclude that more than one round of T cell activation was able to induce additional replication-competent viruses, indicating the possibility that viral reactivation is governed by stochastic processes and that the latent viral reservoir may be larger than initially thought.

398 The Inducible HIV-1 Reservoir Predicted by Combinations of pre- and on-ART Parameters

Anthony R. Cillo; Michele Sobolowski; Elizabeth Fyne; Dianna Koontz; Feiyu Hong; John W. Mellors
University of Pittsburgh, Pittsburgh, PA, US

Background: Antiretroviral therapy (ART) suppresses HIV-1 replication, but an inducible viral reservoir persists in resting CD4+ T (rCD4) cells. We have found that the amount of inducible HIV-1 RNA following *ex vivo* activation of purified rCD4 cells varies 1000-fold across donors. Here, we sought to identify the reasons for this wide variation in inducible HIV-1.

Methods: We studied 10 consecutive HIV-1 infected subjects on suppressive ART with HIV-1 RNA in plasma <50 cps/mL for ≥1.4 years (median: 11 years). Plasma and PBMC were collected and rCD4 cells were purified by negative selection. rCD4 cells were treated for 7 days with anti-CD3/CD28 coated beads and the amount of virus produced was quantified in culture supernatants by qPCR for HIV-1 RNA. We evaluated 9 continuous variables for potential relationships with the amount of inducible HIV-1. Correlations between continuous variables and the inducible reservoir were evaluated by Spearman's correlation. A principle component analysis (PCA) and regression (PCR) were performed using the same 9 variables to identify qualities associated with the amount of inducible HIV-1.

Results: Table 1 shows the 9 variables measured along with the amount of induced HIV-1 per million rCD4 cells. No individual variable correlated significantly with the amount of inducible HIV-1. PCA/PCR was performed to determine the proportion of variation in inducible HIV-1 that could be explained by linear combinations of the 9 variables analyzed. The first 3 dimensions of the PCA explained >80% of the variance in inducible HIV-1. Inducible HIV-1 was positively associated with combinations of pre-ART plasma HIV-1 RNA, residual plasma viremia, and cellular HIV-1 RNA and DNA in PBMC; and inversely associated with CD4 counts at nadir and on suppressive ART.

Table 1. Clinical, immunological and virological characteristics evaluated for comparisons with the inducible reservoir

Subject Number	Pre-ART Parameters				Post-ART Parameters					Size of the Inducible Reservoir (HIV-1 RNA cps/10^6 rCD4 cells)
	Age (years)	Pre-ART HIV-1 RNA (Log_{10} cps/mL)	Nadir CD4 count (cells/mm^3)	Pre-ART CD4 count (cells/mm^3)	Duration of suppression (years)	Cellular HIV-1 RNA (cps/10^6 PBMC)	Cellular HIV-1 DNA (cps/10^6 PBMC)	Residual viremia by iSCA (cps/mL)	Current CD4 count (cells/mm^3)	
1	42	5.0	323	424	1.4	85	457	2.0	605	$8.2x10^{-4}$
2	56	5.6	410	492	13	148	841	1.0	1505	$3.0x10^{-3}$
3	41	4.2	185	326	6.5	10	26	<0.6	607	$6.1x10^{-3}$
4	46	4.0	272	337	3.6	11	148	0.7	465	$1.2x10^{-2}$
5	59	5.1	314	396	17	360	1013	7.8	1023	$3.3x10^{-2}$
6	52	5.0	153	364	17	266	705	1.4	585	$4.0x10^{-2}$
7	59	4.2	80	391	9.5	130	314	5.8	656	$3.6x10^{-2}$
8	52	4.1	231	393	17	6.4	45	<0.4	831	$8.9x10^{-3}$
9	60	3.7	576	900	17	<1	36	<0.7	898	$3.9x10^{-5}$
10	52	4.0	435	486	3.5	192	1093	4.9	895	$2.1x10^{-2}$
Median	52	4.1	293	395	11	385	107	1.2	744	$1.1x10^{-2}$
Interquartile Range	(48 - 58)	(4.0-5.0)	(197 -388)	(371 -471)	(4.3 - 17)	(70.8 - 807)	(10.3 - 181)	(0.43 - 4.2)	(606 -897)	($3.8x10^{-3}$ – $3.0x10^{-2}$)

Conclusions: 80% of the inter-patient variation in the amount of inducible HIV-1 from resting CD4+T-cells was explained by 3 principle components that included pre-ART plasma HIV-1 RNA, residual plasma viremia on ART, cell-associated HIV-1 DNA and RNA levels, and CD4 cell counts pre- and post-ART. This finding supports a model in which no one variable predicts the size of the latent inducible reservoir, but combinations of immunologic and virologic measures explain much of the observed variation in inducible HIV-1.

399 Effects of Antineoplastic Chemotherapy on Dynamics of HIV Population Genetics In Vivo

Sarah A. Watters[1]; Wei Shao[1]; Kieron Dunleavy[3]; Margaret Shovlin[3]; Mark N. Polizzotto[3]; Thomas S. Uldrick[3]; Robert Yarchoan[3]; Wyndham Wilson[3]; Frank Maldarelli[1]
[1]National Cancer Institute (NCI), Frederick, MD, US; [2]National Cancer Institute (NCI), Frederick, MD, US; [3]National Cancer Institute (NCI), Bethesda, MD, US; [4]National Cancer Institute (NCI), Bethesda, MD, US; [5]National Cancer Institute (NCI), Bethesda, MD, US; [6]National Cancer Institute (NCI), Bethesda, MD, US

Background: HIV-1 infection is controlled, but not cured, by combination antiretroviral therapy (cART). Mechanisms of persistence are not well understood although recently a number of groups identified expanded clones of HIV infected cells with proviruses integrated in genes involved in growth promotion. Antineoplastic chemotherapy (CTX) includes agents that target proliferating cells and may therefore have an effect on HIV infected cells. Previously, no long term effects of CTX on levels of total cell associated HIV DNA were detected (Cillo et al., 2013); HIV infects diverse CD4 subsets and differential effects of CTX on structure of HIV populations may occur. We investigated the effects of chemotherapeutic agents on HIV populations in infected individuals undergoing CTX.

Methods: HIV-1 infected patients (N=10) undergoing CTX were identified, and samples were obtained from patients with B cell lymphoma treated with EPOCH-R in the absence of cART (N=6), and from patients with Kaposi's Sarcoma undergoing cART treated with either Paclitaxel or Doxorubicin (N=4). Samples were obtained prior to CTX, during CTX (cycles 1-6) and following CTX completion. HIV single genome sequences (SGS) were obtained, aligned (CLUSTALW), and subjected to phylogenetic and compartmentalization analyses (Simmonds AI, Slatkin-Maddison, and Hudson Population Subdivision tests). Hypermutants and drug resistance mutations were identified using Los Alamos and Stanford Drug Resistance Databases, respectively.

Results: In patients on a regimen of EPOCH-R for B cell lymphoma, in the absence of cART, populations of identical HIV sequences appeared in plasma during chemotherapy with evidence of clonal populations in 2/6 and population subdivision in 1/6 patients. In patients undergoing cART and receiving single agent CTX, no clonal sequences were detected in plasma; clonal populations were detected prior to therapy in cell associated HIV DNA in 4/4 patients on single agent CTX which persisted with no evidence of compartmentalization or population subdivision. No significant change in hypermutant frequency was detected prior to and following therapy in either study.

Conclusions: EPOCH-R during untreated HIV infection resulted in HIV population changes in some patients, suggesting effects of chemotherapy in HIV infected cells. In contrast, single agent chemotherapy had minimal detectable effect on HIV populations.

WEDNESDAY, FEBRUARY 25, 2015

Session P-F5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Gene Editing

400 Targeted Disruption of Essential HIV-1 Proviral Genes by Rare-Cutting Endonucleases

Harshana S. De Silva Feelixge; Nixon Niyonzima; Harlan L. Pietz; Martine Aubert; Dan Stone; **Keith R. Jerome**

Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US

Background: HAART is remarkably successful in suppressing HIV viral load to nearly undetectable levels. However, HAART does not reduce the size of the viral reservoir residing mainly in long-lived memory T cells. Lifelong adherence to HAART is paramount in controlling viral loads. If interruption of therapy occurs, HIV rebounds to pre-HAART viral loads within weeks. In recent years much attention has been focused on developing new methods of gene therapy that have the potential to contribute to HIV cure. Here we evaluate the generation of disruptive mutations within essential HIV-1 proviral genes in order to make the latent HIV pool non-functional. If successful HIV gene disruption can be achieved, reactivation from latency would yield non-viable progeny virus preventing further reseeding of new target cells.

Methods: We developed four zinc finger nucleases (ZFNs) engineered to bind distinct HIV *pol* target sites within protease, reverse transcriptase and integrase. The ZFNs were tested in sup-T1 cells for activity against integrated HIV.

Results: All four ZFNs showed activity in a yeast cleavage assay and against a plasmid-derived HIV genome in HEK293 cells. ZFNs were then delivered to the CD4+ sup-T1 T cell line containing integrated defective HIV-1 provirus (DHIV) using scAAV1 vectors. Two of four ZFNs were able to disrupt integrated DHIV provirus at levels up to 28% in sequences within reverse transcriptase and integrase. To increase the levels of gene disruption cells were treated with the end processing exonuclease Trex2 in combination with HIV-targeted ZFNs. Cells treated with Trex2 showed up to a 2-fold increase in levels of provirus disruption for both ZFNs active against integrated provirus. Treated cells showed reduced production of virus, and molecular cloning and expression of ZFN-induced mutations demonstrated that they efficiently disrupted the ability of HIV to replicate. To further improve disruptive mutagenic events, we also tested another class of rare-cutting endonucleases, megaTALs, which consist of a Transcription-activator like effector (TALE) domain fused to a homing endonuclease. MegaTALs containing 5.5, 6.5 or 7.5 TALE repeats were all able to cleave a plasmid-derived target sequence within the catalytic core domain (CCD) of HIV-1 integrase in HEK293 cells at equivalent levels.

Conclusions: Our data demonstrate the potential of genome editing as a curative therapy for latent HIV infection. Efforts are underway to further increase the frequency of target site disruptions.

401 Enhancing Anti-HIV Gene Therapy: Combining MegaTAL Nuclease Gene Editing With Selection Cassettes

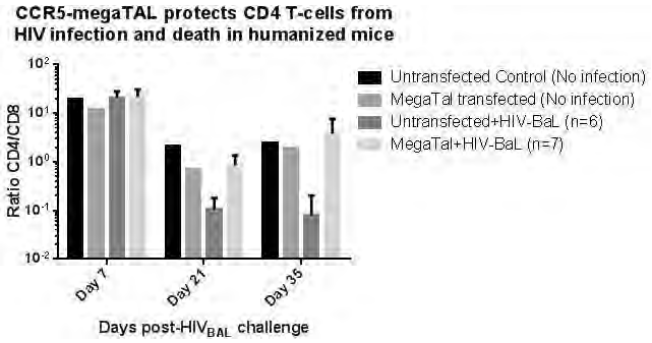
Biswajit Paul[2]; Alexander Astrakhan[3]; Patrick Younan[2]; Blythe D. Sather[4]; Jordan Jarjour[3]; Guillermo Romano[2]; John P. Kowalski[2]; Iram Khan[4]; David J. Rawlings[4]; Hans-Peter Kiem[2]

[1]*Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US;* [2]*Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US;* [3]*BluebirdBio, Cambridge, MA, US;* [4]*Seattle Children's Research Institute, Seattle, WA, US*

Background: Human Immunodeficiency Virus (HIV) infection remains a substantial health problem worldwide. The human C-C chemokine receptor 5 (CCR5) gene, which encodes a co-receptor required for HIV entry into CD4$^+$ T-cells, is a promising alternative therapeutic target. Early clinical trials using CCR5-disrupting zinc finger nucleases in patients have demonstrated sustained functional control of HIV during antiretroviral treatment interruption. However, two limitations of current gene editing required to achieve therapeutic benefit remain unaddressed. These are (a) the need for higher levels of CCR5-disruption in long-term memory cells and (b) preferential selection of gene modified cells protected from subsequent infection during transplant.

Methods: The CCR5-targeting megaTAL is a novel nuclease architecture that combines a LAGLIDADG homing endonuclease scaffold with an eleven repeat transcription activator-like (TAL) effector array to achieve efficient site-specific cleavage. We are coupling megaTAL nuclease treatment with drug selection in order to disrupt the CCR5 locus, and select modified CD4+ T-cells to achieve therapeutically relevant levels of HIV-protected cells. The mutant P140K-O6-methylguanine-DNA-methyltransferase (MGMT-P140K) construct delivers resistance against the drug O6-benzylguanine/1,3-bis(2-chloroethyl)-1-nitrosourea at 50uM O6BG/ 10uM BCNU. The mutant human dihydrofolate reductase (DHFR) construct renders cells resistant to lymphotoxic concentrations of the drug methotrexate (MTX) at 0.05uM. For optimal cell viability we deliver nucleases via mRNA and selection-constructs via adeno-associated virus (AAV).

Results: Electroporation with megaTAL mRNA demonstrated robust CCR5 disruption: 95% in GHOST-Hi5 cell lines and 70-90% in human CD4$^+$ T-cells. Gene-modified human T-cells were transplanted into NOD/SCID/γc-null 'humanized' mice and subsequently challenged with HIV-1 infection. CCR5-null modified cells preferentially survived during active HIV infection *in vivo* (100 fold increase). Primary T-cells transduced with a MGMT-P140K cassette at 60% efficiency showed two-fold expansion over 48-hours *in vitro*. Preliminary data in Jurkat cell lines transduced with a Tyr-22-DHFR cassette at 86% efficiency showed two-fold expansion over 72-hours.



Conclusions: The CCR5-megaTAL nuclease platform produces the highest level of gene-modified CD4$^+$ T-cells reported to date and protects these cells from subsequent HIV infection *in vivo* at significant levels.

402 A Phase I Clinical Trial of Autologous CD4+ T Cells Modified With a Retroviral Vector Expressing the MazF Endoribonuclease in Patients With HIV-1

Jeffrey M. Jacobson[1]; Hideto Chono[2]; Meghan Metz[1]; Gabriela Plesa[3]; Julie Jadlowsky[3]; Simon Lacey[3]; Bruce Levine[3]; Hirofumi Yoshioka[2]; Junichi Minemo[2]; Carl H. June[3]

[1]Drexel University College of Medicine, Philadelphia, PA, US; [2]Takara Bio Inc., Shiga, Japan; [3]University of Pennsylvania, Philadelphia, PA, US

Background: The *E.coli*-derived MazF endoribonuclease specifically cleaves single stranded RNAs at ACA sequences. HIV-1 contains over 240 ACA sequences, making it especially sensitive to MazF activity. In this study, autologous CD4+ T cells are modified using a retroviral vector containing the *mazF* gene expressed under the control of the HIV LTR. MazF expression is thus activated by Tat conditionally during HIV replication. This study is designed to evaluate the safety and durability of MazF-modified CD4+ T (MazF-T) cells, and assess related antiviral effects.

Methods: This is an exploratory Phase I, Open Label, Dual Cohort study evaluating safety, tolerability and immunogenicity of autologous CD4+ T cells expressing the MazF endoribonuclease gene in HIV+ subjects. Both cohorts consist of subjects on combination antiretroviral therapy (cART) with CD4 counts >350 cells/mm^3 and undetectable HIV-1 RNA levels. Subjects in cohort 1 remain on cART throughout the duration of the study. Subjects in cohort 2 participate in a 16 week analytical treatment interruption (ATI) beginning 2 weeks post T cell infusion. All subjects are infused with a single dose of MazF-T cells and are evaluated for persistence of modified cells, impact on CD4 count and effects on HIV viral load.

Results: To date, 4 subjects in cohort 1 have each received a single infusion of 0.5-1x10^{10} cells. There have been no SAE related to MazF-T. All 8 AE related to study drug have been grade 1 in severity. The CD4/CD8 ratio increased in 3 of 4 subjects post infusion, before stabilizing near baseline. Absolute CD4 count remained stable, or slightly increased as compared to baseline. As these subjects remained on cART, all viral loads remained undetectable. MazF DNA signal was detected by qPCR in all 4 subjects' peripheral blood at the most recently available timepoint, including 2 subjects who completed the study at Day 180.

Conclusions: These preliminary results suggest that autologous MazF-modified CD4+ T cells are safe and well-tolerated in aviremic HIV+ subjects and are able to persist out to 6 months post-infusion. Future results in subjects participating in an ATI will further elucidate the anti-HIV effects associated with MazF-T cells in the presence of viremia.

403 CRISPRs Are Able to Efficiently Target Latent HIV and Halt New Infections

Robert Jan Lebbink; Dorien de Jong; Femke Wolters; Emmanuel J. Wiertz; **Monique Nijhuis**

University Medical Center Utrecht, Utrecht, Netherlands

Background: Currently available combination antiretroviral therapy (cART) can successfully control HIV replication. However, conventional treatment lacks the ability to clear the latent reservoir and stop viral production, which remains the major obstacle in achieving a cure. Novel strategies are required to permanently disrupt the HIV genome in the latently infected cells. In this study we have investigated the potential of the CRISPR-Cas9 RNA guided DNA endonucleases system to edit the HIV genome, prevent re-activation from latently infected cells and halt new infections.

Methods: The CRISPR-Cas9 system is comprised of a Cas9 protein, which in combination with a guideRNA (gRNA), is able to cleave a complementary dsDNA sequence. gRNAs were designed to target HIV LTR, protease (PR), reverse transcriptase (RT), integrase (IN) and the structural matrix protein (MA). gRNAs against human B2M, HLA and CD45 were used as controls. The CRISPR-Cas9 system was cloned in a lentivirus vector and used to transduce SupT1 and Jurkat cells. The latter is latently infected with near full-length HIV and expresses GFP upon TNFα stimulation (J.Lat Full Length Clone 15.4). SupT1 cells are transduced with the lentiviral constructs and subsequently infected with HIV using three different MOIs and viral replication was monitored by HIV DNA quantification and HIV CA-p24 production. On and off targeting efficiency (three genes per CRISPR) of the different CRISPRs was assessed by deep sequence analysis.

Results: Lentiviral transduction in SupT1 and Jurkat cells resulted in stable expression of the CRISPR-Cas9 system. Deep sequence analysis demonstrated efficient HIV genome editing (75-99%) and an off-target efficiency ranging between 1.7-0.4%. TNFα –induced HIV reactivation from latently infected T cells was significantly reduced after transduction with CRISPRs specifically targeting the LTR (empty vector 48±2.98% GFP+ cells vs LTR-6 15±6.63% and LTR-4 26± 2.76% GFP+ cells; $p<0.05$). Subsequently, we investigated the potential of CRISPRS targeting the LTR, PR, RT, IN and MA to inhibit viral replication. HIV DNA quantification demonstrated up to 40-fold reduction in intracellular HIV DNA and a significant reduction in virus production ranging from 91-99% inhibition ($p<0.05$).

Conclusions: The newly discovered CRISPR-Cas9 system is able to target HIV efficiently in both primary infection and latency models and may provide a specific, efficacious prophylactic and therapeutic anti-viral approach.

TUESDAY, FEBRUARY 24, 2015

Session P-F6 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HDAC Inhibitors

404 Histone Deacetylase (HDAC) and Histone Acetyltransferase (HAT) Inhibitors Have Opposing Effects on Cellular Susceptibility to HIV Infection

Mark B. Lucera[2]; Curtis Dobrowolski[1]; Jonathan Karn[1]; John C. Tilton[2]

[1]Case Western Reserve University, Cleveland Heights, OH, US; [2]Case Western Reserve University, Cleveland, OH, US

Background: Latency reversing agents (LRA), such as HDAC inhibitors, are being employed as part of a "shock-and-kill" approach to reactivate and eradicate latent proviruses. We recently reported that the HDAC inhibitor vorinostat significantly increases productive viral infection *in vitro*, raising potential concern for its use as a LRA in patients. This effect was also observed with other broad-spectrum HDAC inhibitors as well as the cytoplasmic HDAC6-specific inhibitor tubacin. Our work with HDAC inhibitors led us to hypothesize that treatment with opposing histone acetyltransferase (HAT) inhibitors would subsequently decrease HIV productive infection.

Methods: Primary CD4+ T cells were treated with HDAC/HAT inhibitors and infected with combination reporter or replication competent viruses. Viral fusion and LTR-driven gene expression were measured by flow cytometry. 2-LTR circle transcripts were monitored by PCR and deep sequencing.

Results: Here we report that the HDAC inhibitor vorinostat enhances post-entry infection efficiency 2-3 fold in both single cycle and replication competent experiments. This was found to be a cytoplasmic mechanism in which treatment increased kinetics and efficiency of reverse transcription (RT) and nuclear import of HIV DNA. Recapitulation of this effect with broad-spectrum HDAC inhibitors and cytoplasmic HDAC6 inhibitor tubacin suggest that enhancement of viral infection may be an undesirable effect common to this class of agents. Conversely, treatment with the histone acetyltransferase (HAT) inhibitors garcinol and curcumin was found to significantly reduce LTR-driven EGFP expression in both a time and dose-dependent manner. Additional work is being conducted to ascertain the mechanism of these inhibitors.

Conclusions: Both experiments with HDAC and HAT inhibitors demonstrate that modulating acetylation influences susceptibility of CD4+ T cells to HIV. Our experiments with tubacin suggest that microtubule acetylation may underlie enhanced HIV infection with HDAC inhibitors. We believe our preliminary results with HAT inhibitors demonstrate a proof-of-concept to decrease susceptibility of cells to HIV by directly targeting cellular processes independent of viral heterogeneity and resistance mutations. These findings are of particular significance during HIV transmission where they could potentially be exploited to further reduce the likelihood of spread between individuals.

405 Panobinostat Dosing Has Broad but Transient Immunomodulatory Effects in HIV Patients

Martin Tolstrup[1]; Christel R. Brinkmann[1]; Thomas A. Rasmussen[1]; Rikke Olesen[1]; Anne Sofie Kjær[1]; Mathias Lichterfeld[2]; Charles Dinarello[3]; Lars Østergaard[1]; Ole S. Søgaard[1]

[1]Aarhus University Hospital, Aarhus, Denmark; [2]Ragon Institute of MIT, MGH and Harvard, Boston, MA, US; [3]University of Colorado, Denver, CO, US

Background: To evaluate the immunomodulatory effects from HDACi in HIV-infected patients, we investigated a broad range of immune pathways during a latency reversal trial with panobinostat (PANO). Further, as prolonged epigenetic modulation from HDACi treatment has been raised as safety concern, we evaluated gene expression alterations up to 24 weeks after end of PANO dosing.

Methods: Using flow cytometry, we investigated the impact of PANO on T cell activation (CD69, HLA-DR, CD38), T cell exhaustion (PD-1). Further, levels of activated regulatory T cells and their expression of suppressive markers (CD39 and CTLA4) were assessed. To determine broad changes in immune responsiveness to common stimuli, whole blood stimulations with LPS were performed and inflammatory responses by cytokine release were determined using luminex. Gene expression from purified PBMC's was evaluated using affymetrix HTA 2.0 gene chip.

Results: A rapid increase in proportions of both CD4 and CD8 T cells expressing CD69 were observed ($p<0.01$) as early as 24 hrs after first PANO dosing. This was followed by a marked increase in HLA-DR+ CD4 and CD8 T cells ($p<0.01$) observed at day 4. At the same time point, proportions of activated regulatory T cells increased by 40 % four days after treatment initiation ($p=0.003$) and MFI of the suppressive markers CD39 and CTLA4 increased by 12% ($p=0.009$) and 25 % ($p=0.0002$), respectively. LPS-induced inflammatory responses as determined by IL-1b, IL-12p40, IL-6 and TNF-a secretion were all significantly down regulated four days after dosing. Importantly, all these PANO-induced immunomodulatory effects were reversible and all markers had returned to pre-treatment levels 4 weeks after end of PANO dosing. Lastly, PANO induced significant changes in the overall gene expression pattern (fold-change >1.5, FDR-corrected $p<0.05$). These alterations in gene expression had regressed considerably by week 4 after end of PANO treatment and normalized entirely by week 24 post-PANO therapy.

Conclusions: PANO significantly but transiently influenced T cells activation status, regulatory T cell phenotype and functional mitogen responsiveness. All measures of immune function had returned to baseline levels 4 weeks after completion of PANO and long-term follow-up revealed no sustained effect on overall gene expression. Collectively, the results suggest that PANO does not cause persistent detrimental epigenetic or immunomodulatory changes in HIV patients.

406 Multi-Dose Romidepsin in SIV-Infected RMs Reactivates Latent Virus in Absence of ART

Benjamin Policicchio[1]; Egidio Brocca-Cofano[1]; Cuiling Xu[1]; Dongzhu Ma[1]; Hui Li[2]; George Richter-Haret[1]; Tammy Dunsmore[1]; George M. Shaw[2]; Ivona Pandrea[1]; Cristian Apetrei[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]University of Pennsylvania, Philadelphia, PA, US

Background: Persistent viral reservoirs represent a major obstacle in eliminating HIV-1 in infected individuals, even with ART. One of the reservoir reactivation strategies is the "flush and kill" approach, in which latent virus is reactivated with histone deacetylase inhibitors (HDACi) and eliminated through effective CTL responses. Our goals were to: 1. develop a nonhuman primate model of SIV control with conventional ART; 2. assess the HDACi romidepsin's (RMD) ability to reactivate SIV in controller RMs; 3. assess the effect of CTLs on viral control; 4. develop monitoring capabilities for reactivation studies.

Methods: Four RMs were IV-infected with the SIVsmmFTq infectious molecular clone. All RMs received ART (PMPA; FTC; L-870812) for 9 months from 65 days post-infection. ART was halted and RMD was administered in 3 rounds at 35 day intervals to three RMs, followed by $CD8^+$ cell depletion with a CD8 depleting antibody (M-T807R1). Plasma viral load was monitored with a single copy assay. Cell-associated RNA and DNA were monitored by qPCR. PBMC histone acetylation, IFN-γ production by CTLs and changes in levels of T cells and their immune activation/proliferation status were assessed by flow cytometry.

Results: SIVsmmFTq RMs receiving conventional ART controlled virus replication to <10 copies/ml, without viral blips. At ART cessation, the virus transiently rebounded (up to 10^6 copies/ml), followed by control to undetectable levels (<10 copies/ml), suggesting effective immune control in early treated RMs. RMD administration resulted in significant virus rebounds (up to 10^4 copies/ml) followed by gradual viral decline. RMD was well-tolerated and resulted in a massive surge in T cell activation and a transient decrease of T cells during the first week post treatment. $CD8^+$ cell depletion resulted in a robust viral rebound (up to 10^7 copies/ml) that was controlled upon $CD8^+$ T cell recovery.

Conclusions: We developed a new RM model of virus control with conventional ART and demonstrated that RMD can reactivate SIV *in vivo*. The levels of virus replication, timing of the virus rebound and rapid control of virus replication after RMD administration suggest the reactivated virus is replication-competent and RMD does not persistently alter CTL function. $CD8^+$ cell depletion resulted in higher viral rebound compared to RMD administration, suggesting that RMD did not completely ablate CTL function. Altogether, our results show HDACis can effectively reverse SIV latency.

407 Suberanilohydroxamic Acid (SAHA)-Induced Histone Modifications in the HIV Promoter in a Human, Primary CD4 T Cell Model of Latency

Brian Reardon[1]; Amey Mukim[2]; Savitha Deshmukh[2]; Christopher H. Woelk[3]; Douglas D. Richman[1]; Celsa A. Spina[1]

[1]University of California San Diego, La Jolla, CA, US; [2]VA San Diego Healthcare System, La Jolla, CA, US; [3]University of Southampton, Southampton, United Kingdom

Background: Latently infected CD4 T cells are a major obstacle to HIV eradication with combined antiretroviral therapy (cART). Histone deacetylation at the HIV promoter leads to silencing of viral genes during latency. Use of histone deacetylase inhibitors (HDACi), in the presence of cART, to reactivate viral transcription has been proposed as a means to deplete cellular reservoirs. However, HDACi-induced histone modifications in the promoter of integrated HIV, in association with viral transcription, have not been fully examined in latently infected human primary CD4 T cells. Here, we use a primary T cell model of latency to investigate whether the HDACi SAHA induces histone modifications at the HIV promoter that correlate with HIV activation.

Methods: As described previously (Spina et al. PLoS Pathog. 2013), resting primary CD4 T cells with latent HIV (NL4-3) infection were derived from co-culture with acutely infected, autologous T cells and isolated by flow cytometry. Latently infected cells, from 5 different donors, were treated with 1.2 uM SAHA, anti-CD3/CD28, or vehicle control for 24 hours, in the presence of 0.5uM raltegravir. Induced HIV activation was measured by Tat RNA expression (droplet digital PCR). Histone modifications in the nuc-0 region of the provirus LTR, associated with activation (H3K9 acetylation, H3K4 methylation) or repression (H3K27 methylation), were measured with ChIP-RT-qPCR.

Results: In 3 of 4 SAHA treated donor samples, Tat RNA expression was increased (~1.5 - 2 fold vs. controls); 1 donor sample was not measured due to insufficient RNA recovery. In 4 of 5 SAHA-treated donor samples, histone markers of transcriptional activation were increased and a histone marker of transcriptional repression was decreased compared to control treatment. However, no individual or combination of histone modifications was correlated with Tat expression across donors. Work is ongoing to determine whether examination of histone modifications at earlier time points may produce more definitive results.

Conclusions: While general expected trends in SAHA-induced histone modifications were consistent with detected HIV activation, this preliminary data suggests that induced histone modifications alone are not sufficient to reactivate HIV from latency. Future work will examine whether SAHA affects other essential components for HIV reactivation, such as key transcription factors (SP-1) or P-TEFb activity (via CDK9 phosphorylation), that contribute to HIV reactivation in latently infected cells.

408 Donor-to-Donor Variation in the Host Gene Expression Response to SAHA

Bastiaan Moesker[1]; Brian Reardon[2]; Nadejda Beliakova-Bethell[2]; Akul Singhania[1]; Michael S. Breen[1]; Christopher H. Woelk[1]

[1]University of Southampton, Southampton, United Kingdom; [2]University of California San Diego, La Jolla, CA, US

Background: The "shock and kill" approach to eliminating the latent HIV reservoir depends on efficient reactivation of HIV provirus. Multiple studies have observed variability in the levels of HIV reactivation after treatment of latently infected $CD4^+$ T cells with the histone deacetylase inhibitor SAHA. In this study, we hypothesized that the heterogeneity in HIV reactivation is partly related to donor-to-donor differences that are reflected in host gene expression. Therefore, we sought to identify genes displaying a high level of donor-to-donor variability upon treatment with different doses of SAHA.

Methods: Primary $CD4^+$ T cells from six healthy seronegative volunteers were incubated with 0.34, 1.0, 3.0 or 10.0 μM SAHA for 24 hours, or left untreated, after which RNA was extracted and gene expression was measured using Illumina HT-12 v4 BeadChips. To identify donor-to-donor variation specific to the SAHA treatment, we initially selected only those genes that were expressed at the same level in the untreated condition for each donor, and then ranked genes according to highest variation between donors upon SAHA treatment.

Results: The 100 most variable genes between donors showed higher donor-to-donor variation at the higher SAHA concentrations, 1, 3 and 10 μM compared to 340 nM as determined by Pearson's correlation analysis. Protein interaction network analysis identified STAT1 (interferon-responsive transcriptional activator) and AKT2 (serine/threonine kinase) as "hub" genes within the 100 most variable genes, and gene ontology analysis revealed a cluster of genes whose functions are relevant to HIV latency. Interesting genes identified were JMJD1A, a lysine demethylase involved in hormone-dependent transcriptional activation; EGR2, a zinc-finger protein shown to interact with HIV Tat; SIN3B, a transcriptional repressor of MYC; L3MBTL3 a putative Polycomb group (PcG) protein and chromatin-interacting transcriptional repressor; and NAE1, which has been shown to interact with HIV-1 Vpr. A separate study of 4 donors treated with 1.0 μM SAHA confirmed similar inter-individual variability at the protein level.

Conclusions: It appears that SAHA has different effects in different donors at the level of gene and protein expression. Future work is required to determine if such differences lead to variation in the ability of SAHA to activate HIV in different donors. Future clinical trials with SAHA may need to be tailored to HIV infected individuals likely to respond favorably to this activating compound.

409 Off-Target Effects of SAHA May Inhibit HIV Activation

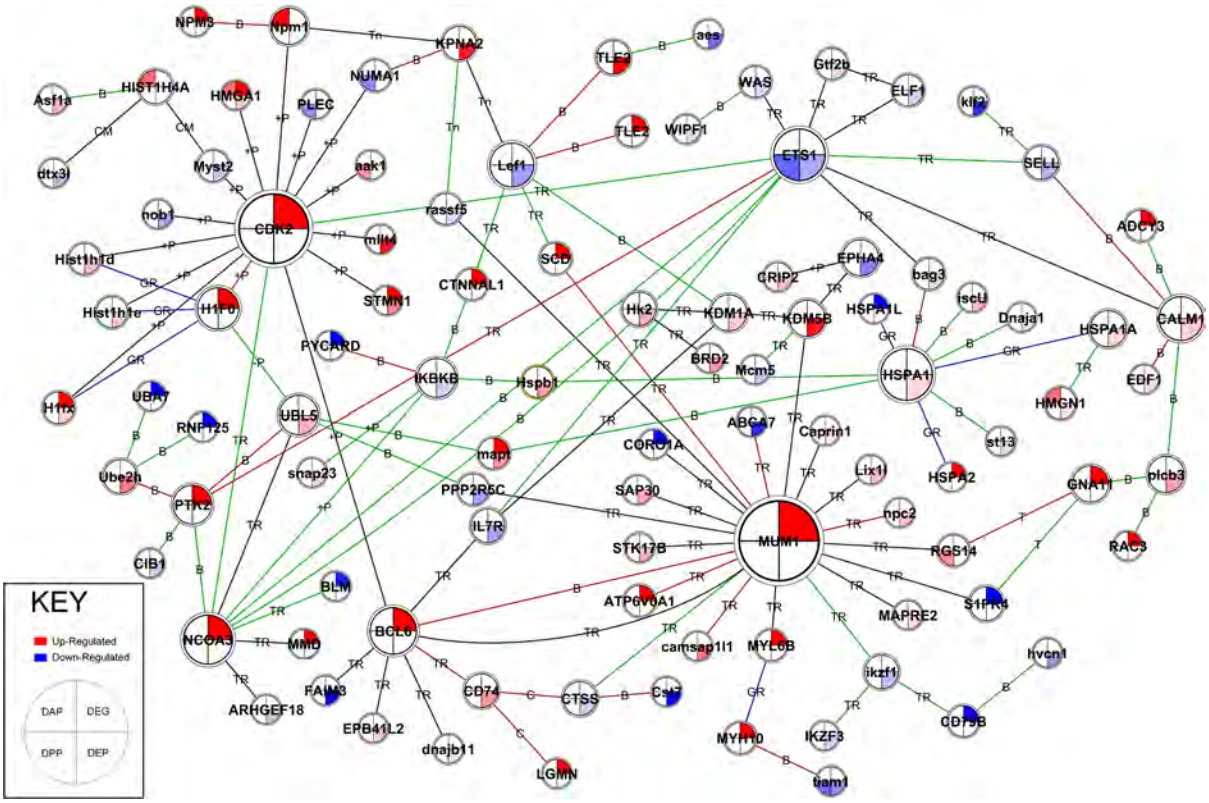
Cory H. White[1]; Harvey E. Johnston[2]; Antigoni Manousopoulou[2]; Celsa A. Spina[1]; Douglas D. Richman[1]; Spiros D. Garbis[2]; Christopher H. Woelk[2]; Nadejda Beliakova-Bethell[1]

[1]University of California San Diego, La Jolla, CA, US; [2]University of Southampton, Southampton, United Kingdom

Background: The latent HIV reservoir is the obstacle to a cure. HIV reactivation with histone deacetylase inhibitors (HDACis) such as SAHA (Vorinostat) in the presence of Highly Active Anti-Retroviral Therapy (HAART) is a candidate eradication strategy. However, the ability of SAHA to activate HIV in clinical trials appears limited. The primary action of SAHA thought to lead to HIV activation is the hyperacetylation of histones, but the off-target effects of this compound have not been well characterized. We have used an integrated systems biology approach (transcriptomics and proteomics) to reveal previously uncharacterized off-target effects of SAHA.

Methods: Primary CD4 T cells were isolated from 10 HIV seronegative donors and either treated with 1μM of SAHA for 24 hours or DMSO (Dimethyl Sulfoxide). Protein extracts from 4 donors were proteolyzed, labeled with iTRAQ 8-plex and characterized by two-dimensional liquid chromatography-mass spectrometry quantitative proteomics. Total RNA was isolated from the samples of 6 donors and subjected to transcriptomic analysis (Illumina HT12 v4 microarrays). Differentially expressed genes (DEGs) and proteins (DEPs), as well as differentially expressed phosphorylated (DPPs) and acetylated (DAPs) proteins were identified using *Limma*. Data integration was facilitated by merging data types and mapping the non-redundant set onto biological pathways, gene ontology terms, and protein interaction networks to characterize the off-target effects of SAHA.

Results: A total of 368 DEGs, 185 DEPs, 18 DPPs, and 4 DAPs (p-value < 0.05) were modulated by SAHA. Data integration suggested that SAHA modulates a number of off-target molecules that may enhance (e.g. AES, HSPA1A, KDM1A) or inhibit (e.g. BRD2, ETS1, HMGA1, INBKB, Lef-1) HIV reactivation. For example, HMGA1, which competes with Tat for TAR binding, was upregulated at the transcription and protein levels and acetylated as the result of SAHA treatment.



Protein Interaction Network (PIN) showing differentially expressed genes (DEG), proteins (DEP), phosphorylated proteins (DPP) and acetylated proteins (DAP) in SAHA treated samples. The image was generated using MetaCore and Cytoscape.

Conclusions: Integration of proteomic and transcriptomic data has revealed a number of off-target effects of SAHA that may hinder activation at the level of the HIV promoter. This sheds light on why combinations of PKC activators and HDACis are more effective than HDACis alone. Future functional genomics studies (*e.g.*, siRNA knockdown) will determine the extent to which the off-target effects of SAHA inhibit viral activation so that they may be circumvented to help design more effective therapies.

410 Bystander Effect of Histone Deacetylase Inhibitors on HIV-1 Infection

Grant R. Campbell; Rachel S. Bruckman; Yen-Lin Chu; Stephen A. Spector

University of California San Diego, La Jolla, CA, US

Background: Histone deacetylase inhibitors (HDACi) are being evaluated in a "shock-and-kill" therapeutic approach to reverse HIV latency from $CD4^+$ T cells. Although administered within the context of combination antiretroviral therapy (cART), infection of bystander cells remains a concern. In this study, we investigated the effect of HDACi on the replication kinetics of HIV within human primary macrophages.

Methods: Monocyte-derived macrophages (MDM) were treated with HDACi (belinostat, givinostat, panobinostat, romidpesin, or vorinostat) at therapeutic doses. The sequential steps of HIV infection and replication were assessed using flow cytometry for receptor expression, HIV p24 ELISA for binding, entry and release dynamics, qPCR for reverse transcription, and Alu-LTR qPCR for integration. The role of autophagy was investigated using small molecule inhibitors including bafilomycin A_1 or by RNAi for *ATG7* or *ATG5*. Cell toxicity was assessed by lactate dehydrogenase release and ssDNA accumulation. Data were analyzed using the Student's *t* test.

Results: None of the HDACi tested had an effect on viral binding, entry, reverse transcription, or integration. Moreover, HIV-replicative fitness post-HDACi treatment was unchanged. However, pre-treatment with HDACi induced a dose-dependent significant decrease in HIV p24 antigen release into the culture supernatants (romidepsin > panobinostat > vorinostat > givinostat > belinostat) ($P < 0.01$). Furthermore, HDACi exposure at the time of infection and at 3, 5, and 7 days post-infection resulted in a significant decrease in HIV p24 antigen ($P < 0.001$) in the absence of cytotoxicity. The inhibition of HIV by HDACi was significantly reduced using RNAi for *ATG5* or *ATG7* and small molecule inhibitors of autophagic flux ($P < 0.05$). Finally, all HDACi induced a significant decrease in intracellular HIV p24 antigen that was dependent upon autophago-lysosome fusion events indicating the degradation of HIV through autophagy.

Conclusions: All HDACi tested induced a dose-dependent degradation of intracellular HIV through the canonical autophagy pathway that requires the formation of autophagosomes and their subsequent maturation into autolysosomes. In contrast, HDACi were found to have no effect on initial infection events including viral entry, binding, and integration. These findings demonstrate that HDACi have important off-target effects that should be considered when being used as part of a cure strategy.

411 HIV-1 Reactivation Increases Mitochondrial Priming of the Latent Reservoir

Jeremy A. Ryan[2]; Allison L. Schure[1]; Zelda Euler[3]; Anthony Letai[2]; **Athe Tsibris**[1]

[1]*Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, US;* [2]*Dana-Farber Cancer Institute, Boston, MA, US;* [3]*Ragon Institute of MIT, MGH and Harvard, Cambridge, MA, US*

Background: Histone deacetylase inhibitors (HDACi) induce cancer cell death through mitochondrial apoptosis, a pathway regulated by the Bcl-2 family of proteins. The extent to which HDACi alter apoptosis priming in non-neoplastic cells is unknown.

Methods: We used BH3 profiling, a flow cytometry-based mitochondrial phenotyping assay, to investigate the mitochondrial priming effects of activation stimuli on peripheral blood mononuclear cell (PBMC) subpopulations. PBMC isolated from HIV-uninfected and HIV-infected, treated, virologically suppressed participants - defined as HIV-1 plasma RNA levels <50 copies/mL for ≥1 year - were studied. Cells were incubated in the presence or absence of anti(a)-CD3/anti(a)-CD28 beads, vorinostat (SAHA), panobinostat (PNB),

or romidepsin (RMD). Dose-ranging studies were performed and, after treatment with a standardized panel of death peptides, BH3 profiles were generated. To determine the selectivity of priming for latently HIV-infected cells, we used the J89 cell line in a series of dual HDACi and small-molecule Bcl-2 inhibitor experiments.

Results: Marked changes in the magnitude and phenotype of $CD4^+$ T cell mitochondrial priming were observed after immune activation or exposure to PNB and RMD, compared to untreated HIV-infected PBMC. BH3 profiles varied as a function of drug type, dose, and duration of exposure. Increased priming in response to the peptide BAD and decreased permeabilization to the peptide NOXAA was observed with both transcriptional and immune activating stimuli, signifying an increased dependence on the anti-apoptotic Bcl-2 protein. The rank order of increased mitochondrial priming was RMD > PNB > a-CD3/a-CD28 beads >> SAHA. Similar magnitudes of priming occurred in central and transitional memory $CD4^+$ T cell subsets. Increasing concentrations of the Bcl-2 inhibitors ABT-263 or -199 in the presence of RMD 20nM led to progressive losses of HIV-expressing J89 cells.

Conclusions: Histone deacetylase inhibition increased primary $CD4^+$ T cell mitochondrial priming and cellular reliance on the anti-apoptotic protein Bcl-2. The mitochondrial phenotypes that we observed were specific to the immune activation or transcriptional re-activation stimulus being used. Combination HDACi and Bcl-2-inhibition selectively eliminated HIV-expressing cells in a latency cell line. Small molecule Bcl-2 inhibition merits further investigation as a targeted HIV eradication strategy.

TUESDAY, FEBRUARY 24, 2015

Session P-F7 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Pharmacologic Latency-Reactivation Agents

412 Reactivation of HIV Latently Infected T Cells by Targeting Tat IRES Translation

Georges Khoury[1]; Sri Ramarathinam[2]; Charlene Mackenzie[1]; David Yurick[1]; Con Sonza[1]; Tony Purcell[2]; Damian F. Purcell[1]

[1]*University of Melbourne At the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia;* [2]*Monash University/Alfred Hospital, Melbourne, Australia*

Background: In virologically suppressed patients, residual latent HIV provirus is predominantly integrated into introns of transcriptionally active genes of memory CD4+ T cells. Much of this provirus is subjected to transcriptional interference, where read-through transcription and splicing incorporate HIV RNA into mature cellular RNAs. We identified the inclusion of Tat first coding exon (Tat-exon2) within a cellular mRNA in latently infected cells, and low level expression of Tat mediated by an Internal Ribosome Entry Site (IRES) present in Tat-exon2. To understand the function of Tat IRES requires a detailed knowledge of the RNA structure and the cellular factors that binds to these chimeric RNAs.

Methods: The folded structure of IRES-active tat mRNA was determined by chemical probing experiments. Cellular proteins binding Tat IRES were purified by fusing 3 binding sites for the MS2 coat protein to the 3'end of tat mRNAs with and without native IRES. The RNP complexes were formed by incubation with a protein extract from a T cell line model of latent infection (J-Lat clone 6.3). The proteins were then identified by 1D SDS-PAGE followed by mass spectrometry analysis.

Results: 2D structure analysis of tat mRNAs by SHAPE revealed that Tat-exon2 harbours an IRES element that folds independently of the 5'UTR region. Sequence alignment of Tat-exon2 from 2233 HIV strains showed highly conserved sequences near the Tat start-codon. We confirmed the role of one conserved element on the IRES-mediated Tat translation by RNA transfection in TZM-bL reporter cells. Silent point mutations within this conserved element that disrupted *tat* mRNA structure induced a significant reduction in virus production measured by quantifying the p24 viral capsid protein by ELISA. Several splicing and translation factors interacting with this *cis*-acting element were identified by mass spectrometry analysis. An important role for these cell proteins in virus protein translation and the reactivation of virion production from latency was determined by over-expression and shRNA knockdown analysis.

Conclusions: Our study revealed an important role for a conserved HIV RNA sequence-structure and several RNA binding proteins in Tat IRES translation. The low level of Tat expression from the IRES element within readthrough transcripts that incorporate latent HIV may participate in residual pathogenesis during treated HIV infection, and constitute potential drug target.

413 Targeting HIV-1 Latency With a Potent Tat Inhibitor

Guillaume Mousseau[1]; Remi Fromentin[2]; Cari Kessing[2]; Lydie Trautmann[2]; Nicolas Chomont[2]; **Susana T. Valente**[1]

[1]*The Scripps Reasearch institute, Jupiter, FL, US;* [2]*The Vaccine and Gene Therapy Institute, Port Saint Lucie, FL, US*

Background: Despite the immense success of HIV anti-retroviral therapy (ART) to reduce replication to very low levels, it fails to eradicate the virus. HIV persists in latently and productively infected $CD4^+$T cells in infected subjects undergoing ART. Thus, we need novel classes of therapeutic agents that target different stages of the virus life cycle to limit latent HIV disease.

Methods: The HIV Tat protein, binds the 5' terminal region of HIV mRNAs, and potently activates transcription. Tat is a very attractive drug target because 1) is expressed early during virus replication, 2) has no cellular homologs and 3) direct inhibition of Tat blocks the feedback loop that drives viral exponential production. Compounds that block Tat have been highly sought after; however, none is yet in the clinic. We have shown that didehydro-Cortistatin A (dCA), an analog of a natural steroidal alkaloid, selectively inhibits Tat-activity with no cellular associated toxicity. dCA binds specifically to the RNA-binding domain of Tat reducing HIV-1 RNA production in infected cultured and primary cells with an EC_{50} as low as 0.7 pM (1).

Results: Here we show that dCA abrogates antigenic virus reactivation from latently infected $CD4^+$T primary cells explanted from patients receiving suppressive ART. dCA can reduce cell-associated HIV-1 RNA production from primary cells and cell-line models of latency by reducing RNA Polymerase II recruitment to the HIV promoter and as a result, cells become refractory to viral reactivation by several anti-latency agents (cytokines, HDAC inhibitors, PKC activators). Furthermore, arrest of dCA treatment does not result in viral rebound, as the promoter is transcriptionally shut-off. As expected, latent cell lines containing virus mutated in either TAR or Tat are insensitive to dCA.

Conclusions: dCA treatment combined with ART may inhibit and persistently abrogate residual HIV production from cellular reservoirs in blood and tissues from virally suppressed subjects, block viral reactivation, reduce reservoir replenishment, and may ultimately decrease the size of the latent reservoir. Our experiments provide a proof-of-concept for the use of transcriptional suppressors in therapeutic approaches for a functional HIV cure.

1. Mousseau et al., Cell Host Microbe (2012). 12(1): 97-108

414 Impact of IFNα-2a on the Replication-Competent HIV-1 Reservoir in CD4+ T Cells

Sara Morón-López[2]; Maria Salgado[2]; Dan Ouchi[2]; Mari Carmen Puertas[2]; Toni Jou[3]; Cristina Tural[3]; Jordi Navarro[1]; Mercedes Perez-Bernal[1]; **Manel Crespo**[1]; Javier Martínez-Picado[2]

[1]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [2]AIDS Research Institute irsiCaixa, Barcelona, Spain; [3]Fundació Lluita contra la SIDA, Barcelona, Spain

Background: Antiretroviral therapy (ART) suppresses HIV-1 progression, but does not eliminate residual viral production of the reservoirs that perpetuate the infection, and constitute the limiting factor for HIV-1 cure. Previous data suggest that IFNα controls HIV-1 replication in patients without ART and decreases proviral DNA in peripheral CD4+ T cells. However, we ignore whether IFNα affects the replication-competent HIV-1 reservoir *in vivo*.

Methods: This open, prospective study included 21 HIV-1 infected ART-suppressed (HIV-RNA<25copies/ml) and HCV-coinfected patients (HCV-RNA>10,000IU/L). Ten patients (IFN group) were treated with pegilated IFNα-2a, pegIFN (180μg/sc/week), and RBV (800-1200mg/d); 11 subjects (control group) did not receive treatment. The replication-competent reservoir was determined by quantitative viral outgrowth assay, at days 0 and 28, and reported as infectious units per million of cells (IUPM). Proviral DNA and cell-associated HIV RNA were quantified by droplet digital PCR, ddPCR, between days 0 and 28 of the study. mRNA expression of APOBEC3G, TRIM5α, TRIM22 and BST2 was measured by qPCR. All parameters were analyzed in peripheral CD4+ T cells.

Results: Subjects' characteristics are summarized in table 1.

Although IUPM did not significantly change between d0 and d28 in any group, pegIFN/RBV administration caused a significant increase in IUPM data dispersion (Levene test, p=0.05), not observed in the control group. These data suggest that pegIFN/RBV perturbs the replication-competent reservoir in peripheral CD4+ T cells.

Longitudinally, we did not observe significant differences in cell-associated HIV-1 DNA copies, neither at d9 nor d28.

Median [IQR] cell-associated HIV RNA decreased significantly in the IFN group (d0: 0.92[0.26-3.29]; d28: 0.25[0.02-0.96]), whereas did not change in the control group (d0: 0.1287[0.07-1.45]; d28: 0.13[0.05-0.42]) (Wilcoxon signed rank test, p=0.0488 and p=0.1934, respectively), suggesting an inhibitory effect of IFN on HIV expression.

APOBEC3G, TRIM5α, TRIM22 and BST2 expression was significantly up-regulated at d9 and d28 in the IFN group, and remained stable in the control group.

Table 1. Subjects' characteristics

	Control group (n=10)	IFN group (n=10)	p value between groups
Age (years), median[IQR][a]	46.5[45.2-52.8]	46.5[41.0-50.5]	0.4300
Females, n(%)[b]	1(10)	2(20)	1.0000
PI based treatment, n(%)[b]	8(80)	7(70)	1.0000
Time since diagnosis (years), median[IQR][a]	23.5[20.2-24.0]	24.0[19.8-25.2]	0.5700
Time of viral load suppression (years), median[IQR][a]	4.5[2.5-5.8]	4.5[2.2-7.8]	0.9400
CD4+ T cell count			
Absolut (cells/μl) day0, median[IQR][a]	447[295-670]	437[218-624]	0.8200
Absolut (cells/μl) day28, median[IQR][a]	570[480-650]	310[203-370]	0.0100
p value (d0 vs. d28)[c]	1.0000	0.0091	
CD8+ T cell count			
Absolut (cells/μl) day0, median[IQR][a]	1,050[1,010-1,200]	650[585-1,130]	0.3700
Absolut (cells/μl) day28, median[IQR][a]	1,190[660-1,310]	440[377-523]	0.0048
p value (d0 vs. d28)[c]	0.8125	0.0313	

[a] p value between groups: Kruskal-Wallis test. [b] p value between groups: Fisher Exact test. [c] p value (d0 vs. d28): Wilcoxon Signed Rank test

Conclusions: PegIFN/RBV perturbs the replication-competent reservoir in peripheral CD4+ T cells and decreases cell-associated HIV-1 RNA, probably through the inhibition of HIV transcription by TRIM22. However, after 28 days of treatment no significant decrease was observed in replication-competent or in proviral DNA reservoir.

415 Immune Modulation With Rapamycin as a Potential Strategy for HIV-1 Eradication

Alyssa R. Martin; Robert F. Siliciano

Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: Despite effective combination antiretroviral therapy (cART), HIV-1 persists in a long-lived latent reservoir in resting memory CD4+ T cells. These latently infected cells represent a major barrier to eradication. A prominent paradigm for HIV-1 cure involves the reactivation of viral transcription in latently infected CD4+ T cells by small molecules. Agents that elicit global T cell activation have been shown to be effective in HIV-1 latency reversal, but cannot be used in a clinical setting due to severe adverse effects associated with this strategy. Due to this toxicity, agents eliciting any level of T cell activation have been avoided in the "shock and kill" approach to eradication, significantly limiting the repertoire of compounds that can be used. The adverse response associated with immune activation is commonly attributed to massive cytokine release by T cells. However, this toxicity may be avoided using concurrent immunosuppressant treatment. The goal of this study was to identify immunomodulatory compounds that inhibit cytokine release and proliferation during a T cell activation approach, without affecting HIV-1 gene expression.

Methods: Resting CD4+ T cells were isolated from HIV-1 infected individuals on effective cART treatment. Cells were treated for 24 hours with αCD3/αCD28 stimulation only, stimulation plus rapamycin or cyclosporin, or a no treatment control. To measure reactivation of latent HIV1, cellular RNA was isolated, reverse transcribed, and qPCR was performed to specifically identify polyadenylated HIV-1 transcripts. Supernatant cytokine release and cell proliferation were assayed by flow cytometry.

Results: We found that rapamycin, an mTOR inhibitor, did not inhibit HIV-1 transcriptional response to αCD3/αCD28 stimulation at concentrations up to 5ug/ml. At these same concentrations, rapamycin was effective at inhibiting pro-inflammatory cytokine release and cell proliferation in response to this stimulation. As expected, the calcineurin inhibitor cyclosporin abrogated both cytokine release and HIV-1 expression induced by αCD3/αCD28 treatment.

Conclusions: Rapamycin downregulates toxic effects of T cell activation without affecting expression of HIV-1. These findings indicate that latency reversing agents that induce some level of T cell activation may be safely and effectively used in the presence of immunomodulators such as rapamycin.

416 Latency Reversing Agents Activate Latent Reservoirs in the Brain of SIV-Infected Macaques

Lucio Gama[1]; Sarah Price[1]; Erin Shirk[1]; Suzanne E. Queen[1]; Ming Li[1]; Brandon Bullock[1]; Stephen Wietgrefe[2]; Luiz Pianowski[3]; M. Christine Zink[1]; Janice Clements[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]University of Minnesota, Minneapolis, MN, US; [3]Bioqual, Valinhos, Brazil

Background: Our group has been testing the PKC activator ingenol-3-hexanoate (Ing-B) as a potential candidate for a "Kick and Kill" HIV eradication strategy. Preliminary data show that Ing-B treatment caused a temporary but significant increase in plasma viral load (VL) of two virally suppressed SIVmac251-infected cART-treated rhesus macaques.

After interrupting the drug regimen (cART and Ing-B), VL stayed undetectable for 45 days before rebounding to pre-cART levels. Here we report results from Ing-B treatment in our consistent and accelerated SIV macaque model for HIV/AIDS and HAND.

Methods: Three pigtailed macaques were dual inoculated with SIVΔB670 and SIV/17E-Fr, and treated at 12 days p.i. with CNS-penetrant cART (TNF, ATZ, RTN, L-870812). After 500 days of viral suppression, one animal was kept as control while two macaques received daily oral doses of Ing-B for 40 days. After a 2-week washout, the same animals received a 10-day treatment of Ing-B in combination with vorinostat (4 daily IV doses in 10 days). Animals were kept on cART until necropsy. SIV RNA was quantitated in plasma and CSF by ddPCR. SIV DNA was assessed in tissues by qPCR. *In situ* hybridization (ISH) for SIV RNA was performed in samples from brain and mesenteric lymph node. Resting CD4+ T cells were collected before and after latency reversing agents (LRA) treatment for quantitative viral outgrowth assay.

Results: LRA induction caused a significant increase of plasma and CSF VL in one of the LRA-treated macaques. CSF viral load was 10x higher than in plasma, and the animal had to be euthanized due to encephalitis-related symptoms. SIV RNA could be detected by ISH in occipital cortex, despite undetectable levels of SIV DNA measured by qPCR. No change was observed in the other LRA-treated macaque. However, the number of SIV-infected resting CD4+ T cells was reduced after LRA-induction in both treated animals when compared to control.

Conclusions: Treatment with LRAs led to a decrease in latent reservoirs in SIV-infected cART-treated macaques. In one animal, treatment activated viral genomes in basal ganglia, leading to CNS disease, indicating that the brain harbors latent virus and should be seriously considered when novel "Kick and Kill" strategies are designed for HIV eradication.

417 TLR7 Agonist GS-9620 Activates HIV-1 in PBMCs From HIV-Infected Patients on cART

Derek D. Sloan[1]; Alivelu Irrinki[1]; Angela Tsai[1]; Jasmine Kaur[1]; Jay Lalezari[2]; Jeff Murry[1]; Tomas Cihlar[1]
[1]*Gilead Sciences, Inc., Foster City, CA, US;* [2]*Quest Clinical Research, San Francisco, CA, US*

Background: Pharmacologic activation of latent HIV reservoirs is considered to be a key part of the strategy towards eradicating HIV-1 infection. GS-9620 is a selective TLR7 agonist currently being evaluated in patients with chronic hepatitis B. Based on recent observations of induced plasma viral RNA and reduction of viral DNA in cART-suppressed SIV-infected rhesus monkeys (RM) treated with a close analog (Whitney *et al*., CROI 2015 submitted), GS-9620 is now also being considered for evaluation in HIV-infected patients. Here we show that GS-9620 activates HIV gene expression ex vivo in PBMCs from HIV-infected patients on cART.

Methods: PBMCs isolated from patients with plasma HIV RNA<50 copies/mL for >12 months were treated with GS-9620 in the presence of ARVs. HIV-1 RNA was quantified in culture supernatants by the AmpliPrep/COBAS® TaqMan® assay. GS-9620-induced cytokines were quantified by Luminex. In selected cultures, CD8 T cell-depleted PBMCs were treated with GS-9620. The effect on the inducible HIV reservoir was assessed by protein kinase C (PKC) agonist-mediated activation of CD4 T cells isolated from GS-9620-treated PBMCs.

Results: In PBMCs from 11 of 12 donors tested, 0.01-1 μM GS-9620 activated HIV RNA expression compared to vehicle control with a 5.8-fold geometric mean maximal activation (range 2.0- to 26.8-fold across donors). Depletion of CD8 T cells increased overall HIV expression without affecting the fold activation induced by GS-9620. While there was no correlation between HIV activation levels and cytokines induced by GS-9620, blocking the type I IFN receptor reduced the maximal HIV expression in all donors assessed (n=4; 85% geometric mean reduction, $p<0.05$). GS-9620 treatment also reduced subsequent PKC agonist-mediated HIV activation (3 of 4 donors; 74% geometric mean reduction, $p<0.05$).

Conclusions: GS-9620 activated HIV RNA expression in PBMCs isolated from patients on suppressive cART, a result consistent with observations in SIV-infected RM treated with a related TLR7 agonist. Type I IFN was required for maximal HIV activation by GS-9620. The HIV response to subsequent PKC activation was reduced in CD4 T cells isolated from GS-9620-treated PBMCs, suggesting a potential reduction in the inducible viral reservoir. Together with the results obtained from SIV-infected RM, these data support the clinical testing of GS-9620 in HIV-infected patients on suppressive cART for possible activation and reduction of the viral reservoir.

418 Baracitinib, Ruxolitinib, Dasatinib Block HIV Replication, Activation, Reactivation

Christina Gavegnano
Emory University, Atlanta, GA, US

Background: HIV-induced activation/inflammation is associated with HIV persistence/reactivation, and is a predictor of morbidity in HIV-infected individuals. HIV-induced activation of myeloid cells promotes trafficking of infected cells to the CNS, and is associated with HIV-induced neurocognitive impairments and HIV-associated dementia. Jak-STAT pathway and tyrosine kinases are activated in macrophages and lymphocytes upon HIV-1 infection, representing attractive cellular targets. As ruxolitinib and baracitinib are Jak1/2 inhibitors either FDA approved or in late phase 3 clinical investigation for myelofibrosis or arthritis respectively, and dasatinib is FDA approved for myeloid malignancies, we evaluated their ability to block 1)HIV replication in primary human macrophages, 2)HIV-induced activation in primary human monocytes and macrophages, and 3)reactivation of latent HIV in T cells.

Methods: Macrophages were treated with various concentrations of ruxolitinib, baracitinib, or dasatinib for 2hr prior to infection (HIV-1_{baL}). Cells were maintained for 6 days before viral quantification (p24-ELISA). Macrophages or monocytes were treated with various concentrations of drug prior to infection (HIV-1_{baL}) and maintained for 3 or 6 days before quantification of HLA-DR, CD163, CCR5 (macrophages), or CD14/CD16 (monocytes). Macrophages and monocytes were treated with various concentrations of drug for 6 days and stained with Near-IR live/dead dye and quantified by FACS. J-lat latent T cells were treated with various concentrations of drug plus TNF-a and reactivation was quantified by GFP reporter 24 hr post induction.

Results: Ruxolitinib, baracitinib, and dasatinib were not cytotoxic (>50 μM for ruxolitinib/baracitinib; 20μM) and demonstrated 1)antiviral potency ranging from 0.001-0.08μM in macrophages, 2)inhibition of HIV-induced upregulation of CCR5, CD163, and HLA-DR (macrophages) and CD14/CD16 (monocytes), and inhibition of reactivation of latent HIV-1 in T cells ($p<0.05$ *versus* no drug controls).

Conclusions: Ruxolitinib, baracitinib, and dasatinib inhibit HIV replication in macrophages, reactivation of latent HIV-1 (T-cells), and HIV-induced activation markers (monocytes/macrophages), which are linked to trafficking of infected cells to the CNS, disease progression, and neurocognitive dysfunction. Selectively blocking Jak-STAT or tyrosine kinase signaling could reverse or prevent HIV-mediated immune activation both systemically and within the brain/CNS.

419 Ex Vivo Identification of Highly Effective Latency-Reversing Drug Combinations

Gregory M. Laird[1]; C Korin Bullen[1]; Daniel I. Rosenbloom[2]; Alyssa R. Martin[1]; Alison L. Hill[3]; Christine M. Durand[1]; Janet D. Siliciano[1]; Robert F. Siliciano[1]
[1]*Johns Hopkins University School of Medicine, Baltimore, MD, US;* [2]*Columbia University, New York, NY, US;* [3]*Harvard University, Boston, MA, US*

Background: HIV-1 persists in a latent reservoir despite ART, and reactivation of this reservoir has been proposed as a cure strategy. Effective drug combinations that achieve high levels of HIV-1 latency reversal will likely be required for a cure. We set out to identify highly effective combinations using resting $CD4^+$ T cells (rCD4s) from infected individuals and use our *ex vivo* measurements to predict *in vivo* efficacy.

Methods: Combinations of latency reversing agents (LRAs) that reverse latency *ex vivo* to an extent approaching the benchmark of maximal T cell activation (~100 fold induction) have not yet been identified. We therefore measured intracellular HIV-1 mRNA levels and supernatant virion production following individual or combination LRA treatment in

rCD4s from infected individuals on suppressive ART. We also determined the effect of LRA treatment on proinflammatory cytokine production. To place our results in broader context and bridge laboratory measures of drug efficacy with clinical trial outcomes, we used a mathematical model to predict the *in vivo* dynamics of viral load following LRA treatment.

Results: We found that PKC agonists synergize significantly with JQ1 and with HDAC inhibitors to induce intracellular HIV-1 mRNA *ex vivo*. Combinations of PKC agonists with JQ1 or an HDAC inhibitor also caused significant virus release – in some instances exceeding that seen with maximal T cell activation. These combinations did not induce the release of proinflammatory cytokines. Using our *ex vivo* measurements of virus production in response to LRAs, we then predicted *in vivo* changes in viral load following LRA treatment. In a realistic clinical scenario, the viral load would be expected to decay immediately after LRA activity ceases. In the most conservative scenario considered by our model, plasma viral loads of over 100 copies/mL are predicted for all treatments we investigated that contain a PKC agonist.

Conclusions: Using multiple assays for latency reversal, we have completed the first *ex vivo* comparative study to identify highly effective LRA combinations. We demonstrated that select PKC agonist–containing combinations reverse latency at levels approaching those seen with maximal T cell activation. We demonstrate that this degree of latency reversal can be achieved without inducing functional T cell activation. Finally, we offer a mathematical framework to predict *in vivo* responses to LRAs using *ex vivo* measurements that can inform the design of future eradication clinical trials.

WEDNESDAY, FEBRUARY 25, 2015

Session P-F8 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Latency Models and Assays

420 Investigating Mechanisms of HIV Persistence Using Droplet Digital PCR Approaches

Elizabeth M. Anderson[1]; Robert Gorelick[2]; Shawn Hill[1]; Catherine A. Rhem[5]; Mary Kearney[1]; John W. Mellors[3]; John M. Coffin[4]; Mike Piatak[2]; Frank Maldarelli[1]

[1]National Cancer Institute at Frederick, Frederick, MD, US; [2]Leidos Biomedical Research, Inc, Frederick, MD, US; [3]University of Pittsburgh, Pittsburgh, PA, US; [4]Tufts University, Boston, MA, US; [5]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

Background: HIV persists at low levels in blood during antiretroviral therapy yet mechanisms of HIV persistence remain poorly characterized. In addition, the transcriptional activity of persistent proviruses is not understood and sensitive quantitative assays are needed to investigate this process. Droplet digital PCR (ddPCR) has been used to detect retrovirus sequences, especially HIV DNA, with single targets of 60-80 nucleotides, however optimal primer-probe combinations to detect the various HIV RNA transcripts have not been defined. We have developed new quantitative assays to explore mechanisms of HIV persistence by measuring its transcriptional activity.

Methods: Primer-probe sets designed to span the TAR region (all transcripts), R-U5 junction (elongated transcripts) and p24 of the *gag* gene (unspliced transcripts) were used to investigate the utility of ddPCR to detect multiple RNA species as well as DNA. RNA transcripts were generated for optimization and to serve as a standard. HIV-1 RNA extracted from virions in cell culture and from patient plasma during rebound viremia were reverse transcribed and assayed. DNA from uninfected CEM and latently infected ACH2 cells were tested. Finally, HIV-1 DNA extracted from PBMCs from patients (N=3) who had ongoing active HIV replication (viral RNA 58,100 to 584,204 copies/mL) was assayed with all HIV primer sets and a CCR5 set to measure total cell DNA.

Results: ddPCR accurately quantified RNA transcripts (mean 1.1-fold difference) and HIV-1 RNA isolated from virions derived from cell culture (mean 1.3-fold difference) based on spec. HIV-1 RNA from patient plasma was detected with all primer sets and showed a 2.6 to 1 ratio of TAR to *gag,* agreeing with the expected 2 to 1 ratio in virions. HIV-1 DNA was undetectable (< 1 copy per 9,000 cells) in the uninfected CEM cells showing no non-specific priming while CCR5 DNA was quantified accurately (1.3-fold difference). For DNA isolated from ACH2 cells, which harbor a single integrated provirus, HIV targets and CCR5 were detected (mean 1.4-fold and 1.1-fold difference). Furthermore, we detected CCR5 DNA (mean 13,520 copies) and HIV-1 DNA for all patients with a mean LTR to *gag* ratio of 1.9 to 1.

Conclusions: ddPCR approaches can distinguish HIV RNA transcription profiles in HIV infected cells, with a broad dynamic range (1-1x10^5 copies) suitable for single cell analyses. Application of these technologies will permit detailed and precise analysis of the mechanisms of HIV persistence in patients undergoing cART.

421LB High-Throughput Single-Cell Quantification of HDACi-Based HIV Reservoir Reactivation

Robert W. Yucha[1]; Emily Hanhauser[2]; Kristen S. Hobbs[2]; Helen Bae[3]; Fatih Inci[4]; Hadi Shafiee[2]; Shuqi Wang[4]; Daniel Kuritzkes[1]; Utkan Demirci[4]; Timothy J. Henrich[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, US; [2]Brigham and Women's Hospital, Cambridge, MA, US; [3]Harvard University, Cambridge, MA, US; [4]Stanford University, Palo Alto, CA, US

Background: Reactivation of latent viral reservoirs is on the forefront of HIV-1 curative strategies. However, little is known about HIV-1 reactivation on a single cell level, such as if reactivation leads to significant increases in the number of transcriptionally active cells, or if increases in cell-associated HIV-1 RNA arise from a smaller, active portion of the reservoir. We therefore designed and implemented a novel microfluidic assay to directly measure the number of cells that produce unspliced (us)RNA from HIV-1-infected individuals on suppressive ART before and after HDAC inhibitor and T cell receptor (TCR) stimulation *ex vivo*.

Methods: Our approach involves high throughput microscale droplet encapsulation of single total or resting CD4+ T-cells (15-45,000) followed by intra-droplet lysis, PCR amplification of HIV-1 usRNA, microscopic or fluorescent flow-based detection, and downstream DNA characterization from isolated droplets. Cells from 4 patients with varied intracellular DNA and RNA levels were stimulated with romidepsin (50nM) or anti-CD3/CD28 antibodies (100ng/mL). We also compared changes in the number of usRNA-producing cells with total usRNA from bulk-cell extracts

Results: The number of usRNA producing resting CD4+ T cells by either manual or automated fluorescent enumeration obtained from 3/4 patients were 4-5 fold higher after T-cell receptor stimulation and 4-7 fold higher after stimulation with romidepsin. However, qPCR demonstrated only a 1.5-10 fold increase in the total amount of usRNA from bulk cell extracts in samples stimulated with either anti-CD3/CD28 or romidepsin. These results may suggest a concordant increase of the number of stimulated cells and usRNA copies per cell. Interestingly, a single patient on suppressive ART with very high caRNA (900,000/10^6 CD4+T-cells) showed only a 1.5-2 fold increase in usRNA producing cells and a decrease (0.3 fold) in usRNA copies per cell post-stimulation.

Conclusions: Our results suggest that latent CD4+ cell activation results in a higher number of cells that produce cell-associated RNA, which correlate approximately with increases in bulk transcriptional activity in samples from 3/4 patients. This study highlights the importance of direct single-cell analysis to fully understand the impact of reactivating agents on latent reservoirs; ongoing studies will further elucidate the relationship between cellular activation and HIV-1 transcription within bulk and single cell environments.

422 Evaluation of HIV-1 Latency-Reversing Agents by a Modified Virus Growth Assay (VOA)

Riddhima Banga; Francesco Procopio; Matthias Cavassini; Alessandra Noto; Song Ding; Giuseppe Pantaleo; **Matthieu Perreau**
Lausanne University Hospital, Epalinges, Switzerland

Background: Inhibitors of histone deacetylases (HDACis) reactivate HIV replication in in vitro models of HIV latency. However, the recent study by Bullen et al. has underscored the difficulty to reactivate HIV-1 latency in primary resting memory CD4 T cells isolated from aviremic long-term treated HIV-1 infected patients (Bullen *et al.*, Nature Medicine 2014). We hypothesized that mimicking the modalities of administration of HDACis in patients in vivo, and in particular, the continuous exposure of primary resting memory CD4 T cells to HDACis in culture would result in efficient reactivation of HIV-1 replication.

Methods: Resting memory CD4 T cells were isolated from 10 aviremic (<20 HIV-1 RNA copies/mL) long-term treated (>2 years) HIV-1 infected subjects and cultured either in the presence of CD3/CD28 (positive control) or continuous exposure to clinically relevant concentrations of HDACis i.e. SAHA, romidepsin, belinostat, panobinostat and givinostat throughout the culture period of 14 days. HIV-1 RNA and p24 protein were measured at the end of the culture period using validated diagnostic tests.

Results: Using the modified VOA, all the HDACis tested (SAHA, romidepsin, panobinostat, belinostat and givinostat) induced reactivation of HIV-1 replication in primary resting memory CD4 T cells isolated from aviremic long-term treated HIV-1 infected patients as indicated by the high levels of HIV RNA and p24 production measured in culture supernatants. Of note, HIV-1 reactivated in the cell cultures was also infectious as demonstrated by the transmission of HIV-1 infection in vitro to CD8-depleted blood mononuclear cells from healthy subjects. Interestingly, givinostat was more potent than the other HDACis in reversing HIV-1 latency in vitro on the basis of the percentage of patients reactivating HIV and the proportion of HIV positive wells. Finally, the combined treatment of anti-CD3/anti-CD28 MAbs plus givinostat did not result in a significant increase of HIV-1 replication, suggesting that both HDACis and TCR signals may target similar populations of latently HIV-1 infected CD4 T cells.

Conclusions: These results support further investigation and development of HDACis in the armamentarium of the therapeutic agents to achieve HIV functional cure.

423 "Kick and Kill" of Latent HIV-1 Infection in Naïve and Central Memory CD4$^+$ T cells

Jennifer M. Zerbato; Nicolas Sluis-Cremer
University of Pittsburgh, Pittsburgh, PA, US

Background: A "kick and kill" strategy, which involves the administration of a latency reversing agent (LRA) to induce HIV-1 out of latency and promote death of the HIV-1-infected cells by cytolytic or viral cytopathic effects, may eradicate the latent HIV-1 reservoir in resting CD4$^+$ T cells. However, the resting CD4$^+$ T cell population is heterogeneous and is composed of distinct subsets that differ in lifespan, proliferative capacity, antigen response time, and in CCR5 and CXCR4 expression levels. It is not known whether the "kick and kill" strategy will be effective in each of the T cell subsets. Therefore, we investigated latency reversal in purified CD4$^+$ naïve (T_N) and central memory (T_{CM}) T cells, which together constitute ~ 70-80% of the resting CD4$^+$ T cell population.

Methods: We developed primary cell models of both R5- and X4-tropic HIV-1 latency in T_N and T_{CM} CD4$^+$ T cells, using a direct infection protocol as described previously (Saleh *et al*. Blood 2007;110:4161). Latency reversal (assessed by extracellular HIV-1 RNA) and concomitant virus-induced cell death was evaluated after exposure to αCD3/CD28 antibodies, PMA/PHA, prostratin or SAHA.

Results: Consistent with previously published data, both R5- and X4-tropic viruses infected T_N cells less efficiently than T_{CM} cells. Consequently, the frequency of latently infected T_N cells was significantly lower than in the T_{CM} cells. Stimulation with αCD3/CD28 antibodies, PMA/PHA or prostratin, effectively reactivated latent HIV-1 in both T cell subsets. When the data were normalized for infection frequency more extracellular virus production was observed in X4-tropic (but not R5) infected T_N cells compared to T_{CM} cells. Interestingly, we found a strong correlation between the number of latently infected cells and extracellular virus production in T_{CM} cells, but not in T_N cells. HIV-1 DNA in both T_N and T_{CM} cells decayed with half-lives ranging from 2.5 to 5.4 days after exposure to αCD3/CD28 antibodies, PMA/PHA or prostratin. In comparison, SAHA was unable to reactivate latent HIV-1 in either T_N or T_{CM} cells, and consequently the latently infected cells persisted after exposure to drug.

Conclusions: We have developed robust primary cell models of HIV-1 latency in CD4$^+$ T_N and T_{CM} cells that can be used to better understand the establishment and reversal of latency in these key reservoirs of HIV-1 infection. Importantly, we demonstrate decay of the latent HIV-1 reservoir in both T cell subsets when the LRA effectively stimulates virus production.

424 HIV Recombination in the In Vitro T_{CM} Latency Model – Reasons and Solutions

Pawel Bonczkowski[2]; Laura J. Martins[1]; Ward de Spiegelaere[2]; Alberto Bosque[1]; Eva Malatinkova[2]; Christopher H. Woelk[3]; Cory H. White[4]; Adam M. Spivak[5]; Vicente Planelles[1]; Linos Vandekerckhove[2]
[1]University Of Utah School of Medicine, Salt Lake City, UT, US; [2]Ghent University and University Hospital, Ghent, Belgium; [3]University of Southampton, Southampton, United Kingdom; [4]University of California San Diego (UCSD), La Jolla, CA, US; [5]Utah University Hospital, Salt Lake City, UT, US

Background: HIV latency research will benefit from *in vitro* latency models that closely mimic *in vivo* latency. The T_{CM} model described by Bosque and Planelles generates high numbers of resting latently infected cells. The initially described model is based on a wild type env deficient virus co-transfected with an HIV env to make a single round virus. Many experiments in our laboratories led to high levels of background infection and massive cell death. These were reminiscent of a spreading infection.

Methods: To assess the replication potential of the virus used in the T_{CM} model, the original complemented virus as well as the culture supernatants of the T_{CM} model were used to transduce Jurkat T-cells and fresh T_{CM}. Subsequently, PCR and deep sequencing were performed to identify recombination as a likely source of replication competent virus. Finally, an adapted model using replication-competent HIV strains carrying EGFP/HSA reporter genes and including cell density manipulations in the presence of ART were assessed to provide a more standardized T_{CM} model.

Results: A spreading infection in the Jurkat and primary cells suggested the presence of a replication competent virus as a cause of background infection and cell death. Experiments with VSV-G and backbone only constructs excluded contamination as the source of this virus. PCR and deep sequencing analysis confirmed the presence of an intact env in the infected cells, indicating that the env deleted constructs recombine with the env sequence used for co-transfection.

An alternative approach using replication competent NL4.3 virus with an IRES-EGFP construct in combination with antiretroviral drugs to block spreading infection proved useful for medium throughput screening of anti-latency compounds. This approach leads to up to 35% of latent infection in the presence of 15% of productive infection. The wild type NL4.3 combined with CD4 expression based cell sorting and cell crowding after infection to promote cell-to-cell HIV transmission can be used for high-throughput assays. Depletion of CD4(-) cells leaves a population of up to 20% latently infected cells with little to no active infection.

Conclusions: Recombination between sequences used to generate single-round vectors in the original model introduces bias to the data and impacts data interpretation. Our study shows that the issue of recombination can be omitted. As an alternative strategy, we propose to use replication competent virus in combination with ARV to generate latently infected T_{CM}.

425 CD4+ Tissue-Resident Memory T Cells Are an Important Reservoir for HIV Persistence

Angela R. Wahl; J. Victor Garcia
University of North Carolina, Chapel Hill, NC, US

Background: Tissue-resident memory T cells (T_{RM}) are a recently described subset of memory T cells present in tissues. Although memory CD4+ T cells are a key target for HIV infection and the major cellular reservoir for HIV in peripheral blood, the contribution of CD4+ T_{RM} to HIV infection and persistence is not known. Currently, studies of T_{RM} in humans are limited to biopsied and cadaveric tissue; T_{RM} do not recirculate and are virtually absent from peripheral blood. Therefore, despite their potential importance to HIV persistence, the effect of HIV infection on the T_{RM} compartment has not been evaluated. To address this critical need, we utilized BLT humanized mice to investigate HIV infection of T_{RM} *in vivo* and establish their contribution to HIV persistence.

Methods: We performed a flow cytometric analysis of peripheral blood and cells isolated from the lymphoid (spleen, lymph nodes, and bone marrow) and non-lymphoid tissues (liver and lung) of uninfected BLT mice and BLT mice infected with a CCR5 tropic HIV-1 strain (JR-CSF, CH040 or THRO). Human memory T cells (CD3+CD45RO+) that expressed CD69 were classified as tissue-resident (T_{RM}). CD25 and HLA-DR negative T_{RM} were classified as resting. T_{RM} were isolated from the tissues of HIV-infected BLT mice by FACS and HIV-DNA and HIV-RNA quantitated by real-time PCR.

Results: As observed in humans, T_{RM} were present in lymphoid and non-lymphoid tissues of BLT mice but virtually absent from peripheral blood ($p<0.0001$). Resting CD4+ T_{RM} were also present in lymphoid and non-lymphoid tissues of BLT mice (mean % of CD4+ T_{RM}= spleen: 27%, lymph node: 61%, bone marrow: 28%, liver: 35%, lung: 33%). During HIV infection, CD4+ memory T cells were significantly depleted from the tissues of BLT mice ($p=0.0002$). CD4+ T_{RM} were also significantly decreased in HIV-infected BLT mice ($p=0.0003$) and preferentially depleted from non-lymphoid tissues (>85% decrease) in comparison to lymphoid tissues (27-55% decrease). Quantitative real-time PCR demonstrated the presence of HIV-DNA and HIV-RNA in CD4+ T_{RM} of all tissues analyzed from HIV-infected BLT mice (mean: $3X10^4$ HIV-DNA and $1X10^5$ HIV-RNA copies per 10^6 cells).

Conclusions: Human T_{RM} are present in BLT mice and their tissue distribution recapitulates the human condition. Importantly, HIV infects and depletes CD4+ T_{RM} in tissues. In addition, T_{RM} contain significant levels of viral DNA and produce high levels of viral RNA. Currently, we are evaluating the contribution of CD4+ T_{RM} to the latent HIV reservoir *in vivo*.

426 HIV-1 Reprograms Resting CD4 T Cells via Foxo1 and L-Selectin Suppression

Benjamin Trinité[1]; Chi N. Chan[1]; Caroline S. Lee[1]; Joy Folkvord[2]; Elizabeth Connick[2]; **David N Levy**[1]
[1]New York University, New York, NY, US; [2]University of Colorado Anschutz Medical Campus, Aurora, CO, US

Background: Forkhead Box protein 01 (Foxo1, FKHR) is a transcription factor central to T cell biology. Foxo1 is necessary for the maintenance of T cell quiescence and for the expression of CD62L (L-selectin), an adhesion molecule that controls T cell migration into lymph nodes. TCR stimulation suppresses Foxo1 activity through PI3K/Akt-dependent phosphorylation of Foxo1 and its relocation to the cytoplasm. Foxo1 inactivation results in CD62L transcriptional repression and the activation or repression of a series of genes that regulate T cell activation, migration, survival, growth and differentiation.

Methods: Purified peripheral blood and tonsil CD4 T cells were infected with HIV-1. Blood and tonsil cells were analyzed by flow cytometry. Blood cells were analyzed by ImageStream (Amnis) for Foxo1 and NF-κB localization and TransAM ELISA (Active Motif) for Foxo1 sequence-specific DNA binding activity. Cellular and viral mRNA were analyzed by TaqMan qRT-PCR.

Results: HIV-1 down-modulated CD62L on productively infected naïve and memory (TCM and TEM) resting CD4 T cells. Partial T cell activation was further revealed by upregulation of the mRNA and surface expression of CD69, a Foxo1-suppressed gene. HIV-1-induced CD62L down modulation was inhibited by the PI3K inhibitors LY294002 and PI-103, indicating that activation of the PI3K/Akt pathway contributes to this effect. ImageStream analysis demonstrated relocation of Foxo1 to the cytoplasm in productively infected resting naïve and memory CD4 T cells, and TransAM ELISA demonstrated loss of Foxo1 transactivation activity. A series of Foxo1 regulated mRNA were decreased or increased in productively infected resting CD4 T cells, including CD62L, IL-7rα, Myc, KLF2, CCR5, Fam65b, $S1P_1$ (EDG1), CD52 and Cyclin D2, indicating a profound reprogramming of these cells by HIV-1. Application of the Foxo1 inhibitor AS1842856 prior to or just after infection accelerated *de novo* viral gene expression and enhanced infected cell viability.

Conclusions: HIV-1 suppression of Foxo1 activity is apparently a strategy to promote its replication in resting CD4 T cells. Dysregulation of Foxo1 may contribute to immune activation, viral load and HIV-1 pathogenesis. As Foxo1 is an investigative cancer therapy target, the ongoing development of Foxo1 interventions may assist the quest to specifically suppress or activate HIV-1 replication *in vivo.*

427 Measurements of Viral Transcription in Elite Suppressor CD4+ T Cells

Christopher W. Pohlmeyer; C. Korin Bullen; Greg Laird; Alyssa R. Martin; Victoria Walker-Sperling; Stanley U. Chioma; Robert F. Siliciano; Joel Blankson
Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: Elite suppressors (ES) are patients who control HIV replication without antiretroviral therapy. Prior studies have shown that the frequency of latently infected cells in these patients is much lower than patients on suppressive antiretroviral regimens. However the frequency of CD4+ T cells that express HIV-1 mRNA at baseline and following T cell stimulation is unknown. In this study we compared HIV-1 transcription levels in CD4+ T cells from chronic progressors (CPs) on suppressive antiretroviral regimens and ES.

Methods: To measure intracellular HIV-1 mRNA, we isolated CD4 T cells from PBMCs of ES and CPs. Replicates of $5x10^6$ cells were stimulated with PMA/ionomycin or DMSO for 24 hours. The cells were collected and lysed in Trizol for RNA extraction and subsequent quantification by qPCR. RNA from supernatants were collected and measured for released HIV-1 mRNA.

Results: A comparison of cell associated HIV-1 mRNA in CD4+ T cells of HAART-suppressed CPs and ES shows that ES have significantly less HIV-1 mRNA per $5x10^6$ cells before stimulation. HIV1 mRNA was uniformly detected in CPs, but was present at very low levels in just 2 of 8 ES ($p>0.05$). When $5x10^6$ CD4+ T cells were stimulated with PMA/ionomycin, the levels of cell-associated HIV-1 mRNA increased in 4 of 7 ES. Additionally, when measuring HIV-1 mRNA levels in culture supernatant following stimulation of 5×10^6 CD4+ T cells with PMA/ionomycin, we detected release of virus from just 2 of 8 ES compared to 5 of 5 CPs. When more replicates were analyzed, viral release was seen in 4 ES. 2 of these patients showed positivity in 1 of 5 replicates ($25x10^6$ cells), releasing approximately 3,000 and 5,000 copies HIV-1 RNA each. Poisson statistics suggests an 89% chance that the signal observed reflects a single cell releasing virus, and our HIV-1 mRNA measurements fit with current estimates of the burst size of an infected CD4+ T cell.

Conclusions: In the present study, we demonstrate that the baseline levels of cell associated HIV-1 mRNA in ES are significantly lower than those observed in CPs per $5x10^6$ cells. However an increase in viral transcription following T cell stimulation was observed. These results further characterize the size of the latent reservoir in ES and confirm earlier studies that suggested that some of these patients are infected with replication-competent virus.

428LB Short-Term Disulfiram to Reverse Latent HIV Infection: A Dose Escalation Study

Julian H. Elliott[1]; James H. McMahon[1]; Wendy Hartogensis[2]; Namandje Bumpus[3]; Christina Chang[4]; Sulggi A. Lee[2]; Jeff Lifson[5]; Peter Bacchetti[2]; Steven Deeks[2]; Sharon R. Lewin[4]
on behalf of the Disulfiram Study investigators

[1]Monash University/Alfred Hospital, Melbourne, Australia; [2]University of California San Francisco, San Francisco, CA, US; [3]Johns Hopkins University, Baltimore, MD, US; [4]University of Melbourne, Melbourne, Australia; [5]National Cancer Institute, Frederick, MD, US

Background: Disulfiram (DSF) is a licensed oral agent, dosed daily and well tolerated in the absence of alcohol. DSF reactivates HIV in a primary T-cell model of HIV latency and had a variable effect on plasma HIV RNA in a pilot clinical study.

Methods: We conducted a prospective dose escalation study. Three cohorts of participants on suppressive antiretroviral therapy (n=10 each) were sequentially enrolled and received DSF daily for three days at doses of 500mg (licensed dose), 1000mg or 2000mg. Baseline samples were obtained at three pre-dosing timepoints (B1-B3); 2, 6 and 24 hours after the first and third doses; and at days 8 and 31. The primary endpoint was cell-associated unspliced HIV RNA (CA-US RNA) in CD4 T-cells. Random intercept negative binomial regression models were used to estimate changes from pre-DSF baseline to timepoints during DSF dosing (days 1-3) and post-DSF. Standard non-compartmental methods were used to estimate pharmacokinetic parameters.

Results: DSF was well-tolerated at all doses. Compared to the mean of three pre-DSF time points, the estimated fold-increases in CA-US RNA during and post-DSF for each cohort were: 500mg: 1.7 (95% confidence interval 1.3 – 2.2) and 2.1 (1.5 – 2.9); 1000mg: 1.9 (1.6 – 2.4) and 2.5 (1.9 – 3.3); and 2000mg: 1.6 (1.2 – 2.1) and 2.1 (1.5 – 3.1) ($p<0.01$ for all). Of the three baseline samples, the third (B3) was collected earlier in the day, prior to first dose. CA-US RNA (but not DNA or plasma RNA) at this timepoint was substantially higher ($p<0.0001$). Using B3 only as the baseline, increases in CA-US RNA during and post-DSF were still observed, but were modest (fold change range 1.0 – 1.6). Compared to the pre-DSF time points, no consistent changes in plasma HIV RNA were noted during dosing, but an increase was seen post-dosing in the cohort receiving 2000mg/day (fold change 1.9 [95% CI 1.3 – 2.7], $p=0.001$). In a post-hoc analysis of the subgroup of participants with high baseline CA-US RNA and high exposure to DSF or its metabolites, there were significant increases in plasma HIV RNA at days 8 and 31 (fold-change ranged from 1.6 – 2.0 ; all $p<0.032$).

Conclusions: Short-term administration of disulfiram resulted in increased CA-US RNA during dosing and up to 4 weeks after the last dose. Possible diurnal variation in baseline CA-US RNA levels was noted, complicating the analysis. The late post-DSF increases in both CA-US RNA and plasma HIV RNA remain unexplained, but are consistent with trends observed with other latency reversing agents.

WEDNESDAY, FEBRUARY 25, 2015

Session P-F9 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Stem Cell Transplantation

429 Impact of Combination of Chemotherapy and Autologous Hematopoietic Stem-Cell Transplantation for Lymphoma on HIV Reservoir Persistence

Heloise Delagreverie; laurence Gerard; Marie Laure Chaix; Marie Laure Nere; Lionel Galicier; Francois Simon; Eric Oksendenhendler; Constance Delaugerre

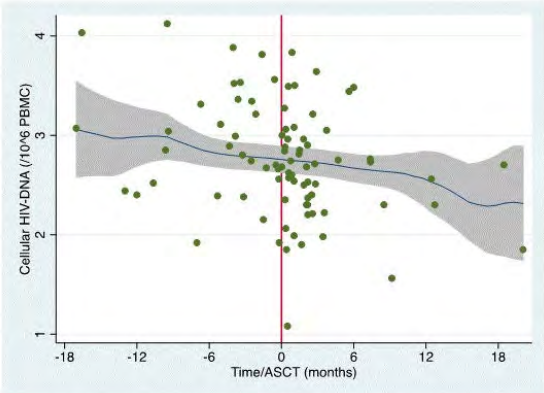
Hôpital Saint-Louis, APHP, Université Paris Diderot, Paris, France

Background: Myeloablation and autologous stem cell transplantation (ASCT) lead to significant depletion of circulating CD4+ T cells and could impact the HIV-1 reservoir. We studied the longitudinal effect of combination chemotherapy and ASCT for HIV-related lymphoma on cellular HIV-1 DNA quantification in patients on suppressive antiretroviral therapy.

Methods: Between 2012 and 2014, we analyzed antiretroviral successfully treated-HIV-infected patients who received intensive myeloablative chemotherapy and ASCT for relapsed or refractory lymphoma. HIV-DNA was quantified longitudinally using sensitive real-time PCR assay (HIV DNA CELL, Biocentric, threshold 5 copies/10^6 PBMC) on frozen whole blood samples at different time points before, during, and after ASCT (D0).

Results: Thirteen patients received a combination of myeloablative chemotherapy and ASCT for lymphoma therapy (Hodgkin = 5, non-Hodgkin = 8). We obtained a total of 84 samples from 18 months before ASCT to more than 6 months after ASCT. Median (IQR) HIV-DNA (n=84) was 2.72 (2.39-3.07) log copies/10^6 PBMC. Median plasma HIV-RNA (n=64) was 1.3 (1.3-1.7) $\log_{10}$ copies/ml and median CD4 cell counts (n=35) was 339 (215-476) cell/mm3. During the follow up, median HIV-DNA was 2.94 (2.44-3.31) $\log_{10}$ copies/ml from -18 to -6 months pre-ASCT, 2.89 (2.66-3.36) from -6 months to ASCT, 2.68 (2.32-2.98) from ASCT to +6 months, and 2.56 (2.30-2.73) after 6 months post ASCT. Evolution of HIV-DNA is shown in the figure.

HIV-DNA decreased during chemotherapy and ASCT according to cellular depletion. However, no significant differences in median HIV-DNA for each patient before and after ASCT were observed (Wilcoxon signed rank sum test, p=ns). In some patients, the proportion of infected cell decreased slightly after 6 months post ASCT. Strong correlation between HIV-DNA and HIV-RNA ($p<10^4$) and no correlation with the CD4 cell count were found.



Conclusions: Despite an important decrease of HIV reservoir during myeloablation due to the severe aplasia, peripheral blood HIV reservoirs persist after cytotoxic chemotherapy and ASCT. In some patients, decrease of the number of HIV infected cell observed after 6 months is probably due to the long-term control of HIV viremia under antiretroviral therapy.

430 HIV-1 Reservoirs and Humoral Immunity in Allogeneic Stem Cell Transplantation Patients

Kathryn E. Stephenson[1]; George H. Neubauer[1]; Emily Hanhauser[2]; Marcelo J. Wolff[3]; Cristian Carvallo[3]; Francisco M. Marty[4]; Steven G. Deeks[5]; Daniel R. Kuritzkes[6]; Dan H. Barouch[1]; Timothy J. Henrich[6]

[1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US; [2]Brigham and Women's Hospital, Boston, MA, US; [3]Clinica Santa Maria, Santiago, Chile; [4]Dana-Farber Cancer Institute, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [5]University of California San Francisco (UCSF), San Francisco, CA, US; [6]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US

Background: Previous studies have shown that HIV-1 reservoirs are reduced following allogeneic hematopoietic stem cell transplantation (HSCT), but that HIV-specific antibodies (Abs) remain detectable over time. It is unknown whether these Abs reflect new responses to occult antigen or the persistence of recipient-derived Abs. Therefore, we characterized HIV-1 reservoirs and evolution of humoral immunity in 6 allogeneic HSCT patients with wild-type (WT, N=4) and *CCR5*Δ32/Δ32 (N=2) donors.

Methods: IgG binding titers to a panel of 9 gp140 trimers of different clades by ELISA and quantitation of HIV-1 reservoirs were performed. IgG binding signatures were measured by novel peptide microarray containing 6,564 peptides covering the entire HIV-1 proteome.

Results: Like the previously described Boston and Berlin patients, an additional subject who received *CCR5*Δ32/Δ32 donor cells had no detectable cell-associated HIV-1 DNA and RNA 3.4 months after HSCT in the setting of ART. HIV-1 DNA levels also markedly decreased in 2 other patients within 8 months following WT HSCT. Despite these reductions in viral reservoirs, HIV-1-specific Ab titers and binding signatures were detectable in all patients at all time points, up to 5 years post-HSCT, though the magnitude of responses steadily declined over time. In 2 patients with baseline samples, pre-HSCT Ab signatures were detected following WT transplantation and did not evolve over 6-8 months of follow-up, suggesting that recipient-derived HIV-1-specific Abs persist post-HSCT. In Boston patients A and B, the Ab signature detected 2-4 years post-HSCT did not evolve until treatment interruption and viral rebound, at which point both signatures acquired new Env specificities suggestive of donor-derived acute Ab responses. The Ab signature of the Berlin patient 3 years post-HSCT remained unchanged over a 2 year period. In both *CCR5*Δ32/Δ32 HSCT patients, Env gp140 Ab levels were 0.5-1 log lower than WT HSCT patients at the same time points.

Conclusions: Viral reservoirs are substantially reduced within 8 months by allogeneic HSCT with WT or *CCR5* Δ32/Δ32 donor cells. Nevertheless, our data suggests that recipient-derived HIV-1-specific Abs may persist for years, despite the lack of recipient peripheral B cells or detectable antigen stimulus. Characterization of these Abs may provide insight into tissue lymphocyte and HIV-1 persistence, and a better understanding of durable immune memory.

431 Breakthrough of Preexisting X4-Capable HIV After Allogeneic Stem-Cell Transplantation

Jens Verheyen[1]; Alexander Thielen[2]; Miriam Dirks[1]; Nadine Lübke[3]; Marek Widera[1]; Lambros Kordelas[1]; Martin Däumer[2]; Rolf Kaiser[3]; Stefan Esser[1]

[1]University Hospital Essen, University Duisburg-Essen, Essen, Germany; [2]Institute of Immunology and Genetics, Kaiserslautern, Germany; [3]University of Cologne, Cologne, Germany; [4]University Hospital Essen, University Duisburg-Essen, Essen, Germany; [5]University Hospital Essen, University Duisburg-Essen, Essen, Germany

Background: Recently, we reported the case of an HIV-infected patient diagnosed with T-cell lymphoma who subsequently underwent allogeneic stem-cell transplantation (alloSCT) from a CCR5 delta32 homozygously mutated donor. In this case HIV replication could not be controlled by the immune system and the patient died after a relapse of the T-cell lymphoma. So far, the evolutionary pathways of the HIV tropism in this patient has remained unclear.

Methods: The tropism of HIV was analyzed from viral RNA and proviral DNA using the Illumina MiSeq platform for deep sequencing of gp120 V3. Samples were taken before (-287d: RNA, -103d: RNA/DNA) and after alloSCT (+20d: RNA, +280d: DNA, +373d: RNA). Viral tropism was predicted by using $\text{geno2pheno}_{[\text{coreceptor}]}$ indicating the probability of classifying a R5-tropic virus falsely as a CXCR4-capable virus (FPR).

Results: Several distinct virus populations could be observed before and after alloSCT, which harbored specific mutational patterns (I14L, A19V, G24-, H34Y). Before alloSCT two virus populations were dominantly found in viral RNA and DNA only distinguished by mutation (R18K) with FPR of 10.5 (R18wt) and 8.5 (R18K), respectively. Apart from these two virus populations several minority variants could be detected carrying additional amino acid substitutions (N7S, K10R, H13T, R18W, Q32K, H34F) resulting in FPR from 7.8 to 4.2. These minority variants were especially detected in proviral DNA (-103d). One HIV variant detected in proviral DNA (4.4%) before alloSCT (-103d) had a unique mutational pattern (S11A, H13T, I14L, A19V, F20Y, T21K, Q32K) classified as clearly X4-capable (FPR 0.4). This sequence was identical to the sequence of the dominant HIV variant replicating in the patient after alloSCT. Overall, the viral variability was limited in sequences obtained after alloSCT from viral RNA and proviral DNA. Only a small fraction of the virus population displayed further unique amino acid substitutions marginally influencing the FPR (FPR 0.2: H13A, I26T and I26V, respectively; FPR 0.5: A19I; FPR 0.7: G28E).

Conclusions: The selective pressure exerted by the transplantation of allogeneic stem-cells homozygous for the CCR5 delta32 mutation resulted in the selection of already preexisting X4 capable HIV. Even the presence of only a minor X4 variant before alloSCT prevented the control of HIV in the absence functional CCR5 receptor.

432 Allogeneic Transplantation With CCR5 Δ32/Δ32 Cord Blood Hematopoietic Cells in an HIV-1-Infected Patient

Rafael Duarte[1]; **Maria Salgado**[2]; Isabel Sanchez-Ortega[1]; Sara Morón-López[2]; Maria C. Puertas[2]; Lawrenze D. Petz[4]; Sergi Querol[3]; Bonaventura Clotet[2]; Javier Martínez-Picado[2]

[1]Institut Català d'Oncologia, L'Hospitalet del Llobregat, Spain; [2]IrsiCaixa Institute for AIDS Research, Badalona, Spain; [3]Barcelona Cord Blood Bank, Barcelona, Spain; [4]StemCyte International Cord Blood Center, Covina, CA, US

Background: The Berlin patient provides the only evidence to date of long-term control of HIV-1 infection after an allogeneic hematopoietic cell transplantation (HCT). Low prevalence of Δ32/Δ32 genotype (<1%) made the search for "patient number 2" unsuccessful for years. Since just a 4/6 match is necessary for cord blood transplantations (CBT), chances to find a *CCR5* Δ32/Δ32 donor are higher. Here, we describe a case of allogeneic HCT using *CCR5* Δ32/Δ32 cord blood (CB) cells in a patient with diffuse large B-cell lymphoma (DLBCL) and HIV-1 infection.

Methods: The myeloablative CB alloHCT was performed using *CCR5* Δ32/Δ32 CBU (from Stemcyte) plus $CD34^+$ cells from a haploidentical brother. HIV-1 reservoir was measured before and post-transplantation. qVOA was performed in peripheral $CD4^+$ T cells. Total cellular HIV-1 DNA and cell associated RNA was determined with ddPCR. Viral tropism was genotypic and phenotypically determined.

Results: A 36 year-old man with antiretroviral-treated HIV-1 infection from 2009 was diagnosed with DLBCL stage IIA in 2012. At that time, plasma viral load was 2.5 log copies/mL (single copy assay), and the replication competent reservoir size was of 1.2 copies/10^7 peripheral $CD4^+$ T cells. Indeed, viral reservoir was detected as HIV-1 DNA and cell-associated HIV-1-RNA in peripheral $CD4^+$ T cells, as well as HIV-1 DNA in GALT and free HIV-1-RNA in cerebrospinal fluid. Patient's virus was CCR5-tropic and no minor CXCR4-tropic strain was detected. During HCT, ART continued with abacavir, lamivudine and raltegravir. Chimerism reached 100% by day +73. At this point, the patient became *CCR5* Δ32/Δ32. Ultrasensitive SCA viral load analysis decreased right after HCT, reaching minimal levels at the time of full CB-chimera. No HIV-DNA was detected using ddPCR quantification or semiquantitative tests of amplification, and recipient CD4+T cells responded to stimuli but were not able to generate a productive infection *in vitro* after spinoculation with laboratory viral strains, or the patient's viral isolate. Regretfully, the patient developed an aggressive DLBCL progression followed by very rapid clinical deterioration and died from disease progression three months after HCT.

Conclusions: This data suggest that *CCR5* Δ32/Δ32 CB HCT can successfully eliminate HIV-1 and render the recipient's T cells resistant to HIV-1 infection. This strongly support the use of CB as a platform for a broader application to other HIV-1 infected individuals with severe hematological malignances.

433 CCR5 Editing in Hematopoietic Stem Cells in a Nonhuman Primate Model of HIV/AIDS

Christopher W. Peterson[1]; Jianbin Wang[2]; Patricia Polacino[3]; Michael C. Holmes[2]; Shiu-Lok Hu[3]; Philip D. Gregory[2]; Hans-Peter Kiem[1]

[1]*Fred Hutchinson Cancer Research Center, Seattle, WA, US;* [2]*Sangamo BioSciences, Inc., Richmond, CA, US;* [3]*University of Washington, Seattle, WA, US*

Background: Hematopoietic stem cell (HSC) transplantation remains the only clinically observed path to functional cure of HIV infection. To better understand the mechanism of HSC-driven HIV control, and apply this therapy to a greater number of patients, we have developed a model of combination antiretroviral therapy (cART)-suppressed HIV infection in the pigtailed macaque, applicable to both gene therapy- and allogeneic transplant-based cure strategies. Following transplantation of HIV-resistant, autologous cells into conditioned animals, we are evaluating the extent to which protected cell progeny impede infection by SIV/HIV (SHIV) chimeric virus *in vivo*.

Methods: Animals are challenged with SHIV virus containing an HIV envelope, after which a 3-drug cART regimen is initiated. Autologous HSCs are engineered to resist infection through targeted disruption of the CCR5 genetic locus using Zinc Finger Nucleases (ZFNs). Engraftment, persistence, and SHIV response of these autologous stem cells and their progeny are measured *in vivo*.

Results: SHIV infection results in sustained viremia with consequent reductions in $CD4^+$ T cells in peripheral blood and secondary lymphoid tissues. Moreover, administration of three-drug cART leads to rapid and durable suppression of plasma viremia to <30 copies/mL plasma - suggesting that this model recapitulates key features of HIV infection and treatment in humans. CCR5 targeting experiments yield up to 60% gene disruption in $CD34^+$ cells *ex vivo*, translating to approximately 5% disruption *in vivo* following transplant. Importantly, up to 10% of transplanted cells carry two disrupted alleles of CCR5; these cells should preferentially reconstitute $CD4^+$ T-cell pools and other susceptible subsets following SHIV challenge. Consistent with this prediction, our preliminary data suggest that CCR5-deleted cells undergo positive selection following SHIV challenge *in vivo*.

Conclusions: Our pigtailed macaque model of HIV infection and cART represents a promising platform for modeling functional cure strategies. Here we show that CCR5 deletion does not impair HSC engraftment or differentiation, and that CCR5-deleted cells may undergo SHIV-dependent positive selection even when present at low levels. Our model enables the evaluation of novel therapeutic approaches in the clinically relevant context of cART controlled SHIV infection - a setting of particular importance to approaches aimed at addressing the viral reservoir.

434 Cytoxan Enhancement of SB-728-T Engraftment: A Strategy to Improve Anti-HIV Response

Gary Blick[2]; Jay Lalezari[3]; Ricky Hsu[4]; Erin DeJesus[5]; Trevor Hawkins[6]; Ronald T. Mitsuyasu[7]; Shelley Wang[1]; Gary Lee[1]; **Winson Tang**[1]; Dale Ando[1]

[1]*Sangamo BioSciences, Inc., Richmond, CA, US;* [2]*CIRCLE CARE Center, Norwalk, CT, US;* [3]*Quest Clinical Research, San Francisco, CA, US;* [4]*New York University School of Medicine, New York, NY, US;* [5]*Orlando Immunology Center, Orlando, FL, US;* [6]*Southwest Care Center, Santa Fe, NM, US;* [7]*University of California Los Angeles CARE Center, Los Angeles, CA, US*

Background: Administration of CCR5 modified autologous CD4 cells (SB-728-T) is safe and well-tolerated and results in increases in total CD4 counts. The modified cells traffic to lymphoid tissues and have a selective survival advantage during ART treatment interruption (TI). Studies in CCR5 Δ32 heterozygote HIV subjects showed VL reductions during TI correlated with levels of engraftment of circulating bi-allelic CCR5-modified cells supporting the importance of maximizing engraftment of modified cells. We have previously presented preliminary data on the use of low dose cyclophosphamide (CTX) to enhance this process. We now report the final results of this dose ranging study.

Methods: A dose escalation study of IV CTX, with doses ranging from 100 mg/m^2 to 2 g/m^2 (n=3-6/cohort), administered 1-3 days prior to SB-728-T (>90% CD4, <1% CD8) infusion was performed in 18 aviremic, ART-treated HIV subjects with CD4 T cells > 500/uL.

Results: CTX was well tolerated with low grade GI side-effects at doses up to 1 g/m^2. Grade 3 and 4 neutropenia requiring G-CSF developed at 1.5 and 2.0 g/m^2 CTX. A dose-related increase in CD4 count and engraftment of bi-allelic CCR5 modified cells was observed with CTX doses up to 1 g/m^2 but did not increase at 2.0 and 1.5 g/m^2. By comparison, there was a progressive decline in CD8 cells with CTX dose escalation. Data in the table is expressed as Mean $\pm$ SE; changes as Day 7 relative to pre-treatment baseline.

A 1-log VL reduction from peak was seen in 1 subject each at 100 and 500 mg/m^2 of CTX while 1 subject each at the 1 and 1.5 g/m^2 dose level had a 2-log decline during TI. At the conclusion of the study, 3 additional subjects were conditioned with 1 g/m^2 of CTX and administered CCR5 modified T cells containing 40.5$\pm$5.6% CD4 and 46.9$\pm$6.4% CD8 T cells. CD8 count increased by a mean of 2590/uL at 7 days in the 2 subjects with data available for analysis. The VL in the first subject remains undetectable 5 weeks after TI initiation versus a median duration of 15$\pm$3 days in subjects who received only SB-728T.

	CTX 100 mg/m^2	CTX 500 mg/m^2	CTX 1 g/m^2	CTX 2 g/m^2	CTX 1.5 g/m^2
ΔCD4 (cells/uL)	776 ± 502	1695 ± 518	2700 ± 966	1370 ± 721	1396 ± 367
ΔCD8 (cells/uL)	98 ± 49	180 ± 117	-210 ± 7	-424 ± 63	-164 ± 161
Bi-allelic (cells/uL)	55 ± 42	102 ± 24	169 ± 67	142 ± 30	180 ± 25

Conclusions: CTX conditioning is well tolerated and was associated with increased engraftment of CCR5-modified T cells at doses up to 1 g/m^2 in HIV subjects. CTX conditioning may be a useful strategy to maximize the engraftment and anti-viral effects of SB-728-T. The effects of co-administering CD8 cells with SB-728-T on VL will be presented.

TUESDAY, FEBRUARY 24, 2015

Session P-G1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

CNS Reservoirs

435 Highly Precise Measurements of HIV DNA in CSF and Blood by Droplet Digital PCR

Michelli Faria de Oliveira[1]; Sara Gianella[1]; Scott Letendre[2]; Konrad Scheffler[1]; Sergei L. Kosakovsky Pond[1]; Davey M. Smith[1]; Matt Strain[1]; Ronald J. Ellis[2]

[1]*University of California San Diego, La Jolla, CA, US;* [2]*HIV Neurobehavioral Research Center, San Diego, CA, US*

Background: We investigated associations between HIV DNA reservoir dynamics in cerebrospinal fluid (CSF) and blood in subjects with or without antiretroviral therapy (ART), to better understand the dynamics of these critical targets for eradication, and to gauge how well the HIV DNA reservoir in anatomic compartments can be predicted by measurements in peripheral blood.

Methods: We analyzed paired peripheral blood mononuclear cells (PBMC) and CSF cell pellets from 29 chronically HIV infected subjects with or without ART. Genomic DNA was extracted from PBMC using silica-based columns, while CSF cell pellets were directly lysed. Levels of HIV DNA (pol gene) were measured by digital droplet PCR (ddPCR) and normalized to cell numbers measured with RPP30. Non-parametric tests of associations between levels of HIV DNA and RNA in CSF and blood were carried out.

Results: We investigated 20 subjects with undetectable HIV RNA (<50 copies/ml in blood plasma and CSF) and 9 subjects with detectable HIV RNA (median of 4.22 log_{10} HIV RNA in blood and 4.11 log_{10} HIV RNA in CSF). The median CD4 count was 498 (interquartile range [IQR]: 362-637). Patients on ART were mostly on regimens including a protease-inhibitor (86%) had a median time of ART exposure of 6.2 years (IQR: 4.6-11.6) and a median CNS penetration effectiveness (CPE) value of 7 (IQR: 7-7.8). HIV DNA was detected in 19 (66%) CSF pellets, including 10 (50%) samples in which HIV RNA was undetectable in CSF. HIV DNA levels in CSF cells positively correlated with HIV DNA levels in PBMC (P=0.03) and with HIV RNA in CSF (P=0.05) but not with the number of CSF leukocytes. Levels of HIV DNA in PBMC positively correlated with HIV RNA levels in blood (p=0.001). Similarly, the levels of HIV RNA significantly correlated between both compartments (P<0.0001). Interestingly, while levels of HIV DNA in blood were significantly lower in subjects on suppressive ART compared to untreated participants (P=0.01), HIV DNA levels in CSF did not differ between treated and untreated participants.

Conclusions: Levels of HIV DNA and RNA correlated within and between blood and CSF compartments. However, suppressive ART was associated with lower HIV DNA levels in blood but not in CSF cells, despite relatively high CPE values. The HIV DNA reservoir in the CNS may not be effectively targeted with highly potent ART.

436 Antiretroviral Concentrations in Brain Tissue Are Similar to or Exceed Those in CSF.

Namandjé Bumpus[2]; Qing Ma[4]; David J. Moore[1]; Brookie M. Best[1]; Ronald J. Ellis[1]; Cristian L. Achim[1]; Melanie Crescini[1]; Courtney Fletcher[3]; Igor Grant[1]; **Scott Letendre**[1]
The CNTN Group
[1]University of California San Diego, San Diego, CA, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]University of Nebraska Medical Center, Omaha, NE, US; [4]University at Buffalo, Buffalo, NY, US

Background: Limited distribution of many antiretroviral therapy (ART) drugs into the central nervous system (CNS) results in much lower drug concentrations in cerebrospinal fluid (CSF) than in blood. Estimates of CSF distribution have been linked to HIV RNA levels in CSF and neurocognitive performance but results can be inconsistent. One possible reason for this inconsistency is that ART drug concentrations in CSF may not accurately reflect those in brain tissue. The objective of this analysis was to measure ART drug concentrations in brain tissue collected from adults dying with HIV disease.

Methods: 9 HIV+ adults were evaluated in the California NeuroAIDS Tissue Consortium (CNTN) within 6 months of death; reported taking ART at that antemortem visit; and had detectable concentrations of at least one ART drug in serum at autopsy. Autopsies were performed within 30 hours of death. Brain tissue was collected and stored at -80°C. Concentrations of 6 ART drugs (see Table) were measured in 3 brain tissue regions, globus pallidus (GP), cortical gray matter (CGM), and white matter (WM), by LC/MS with a lower limit of quantitation of 25 ng/mL.

Results: Subjects were mostly men (82%) with a mean age of 40.4 (SD 5.0). The most common cause of death was pneumonia. ART drug concentrations in brain tissue in ng/mL are summarized in the Table. Concentrations of ATV, EFV, FTC, and 3TC were similar to published concentrations of these drugs in CSF but concentrations of TDF were higher than reported values in CSF. LPV concentrations in brain tissue were also higher than reported in CSF but only in WM. Drug concentrations appeared to vary by brain region: Across all drugs, concentrations were lower in CGM than in the other two regions (p=0.01, paired signed rank test).

	n	Overall Mean	WM (mean)	GP (mean)	CGM (mean)
Atazanavir (ATV)	2	< 25	< 25	< 25	< 25
Efavirenz (EFV)	2	38.6	45.2	34.8	35.9
Emtricitabine (FTC)	4	181.3	230.4	173.2	140.3
Lamivudine (3TC)	3	196.9	205.5	209.8	175.4
Lopinavir (LPV)	4	153.3	410.6	< 25	< 25
Tenofovir (TDF)	6	206	220	212.1	185.8

Table. Summary of Antiretroviral Concentrations in Brain Tissue.

Conclusions: This is the first analysis of ART drug concentrations in human brain tissue. Concentrations of most drugs in this small analysis were similar to reported concentrations in CSF but TDF had higher concentrations than expected based on CSF reports. Regional variation in ART drug concentrations may be important for antiviral efficacy and toxicity.

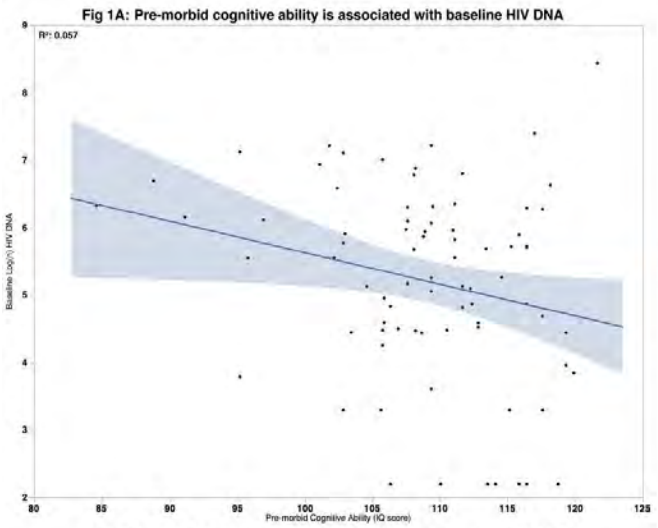
437 HIV DNA Peripheral Reservoirs Have a Nonlinear Impact on Brain Pathology

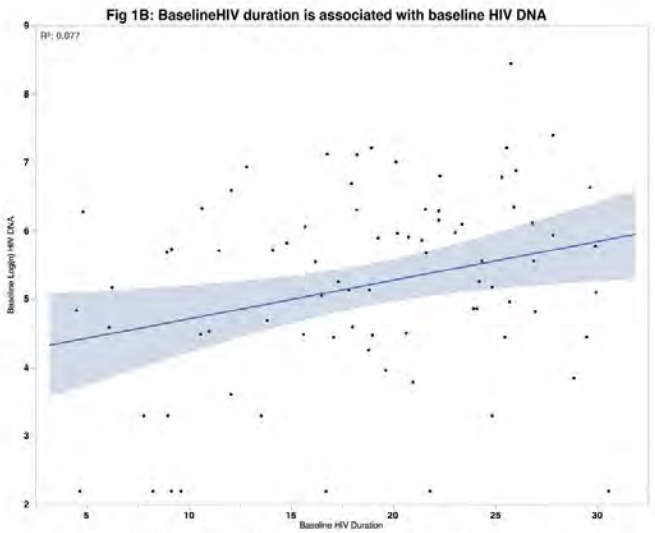
William Hey-Cunningham[2]; Nadene Dermody[3]; Phillip Chan[4]; Bruce Brew[5]; Kersten Koelsch[2]; **Lucette A. Cysique**[1]
[1]NeuRA, University of New South Wales, Randwick, Australia; [2]Kirby Institute, University of New South Wales, Sydney, Australia; [3]Macquarie University, Sydney, Australia; [4]Queen Elizabeth Hospital, HKSAR, Hong Kong, China; [5]St. Vincent's Hospital, University of New South Wales, Sydney, Australia

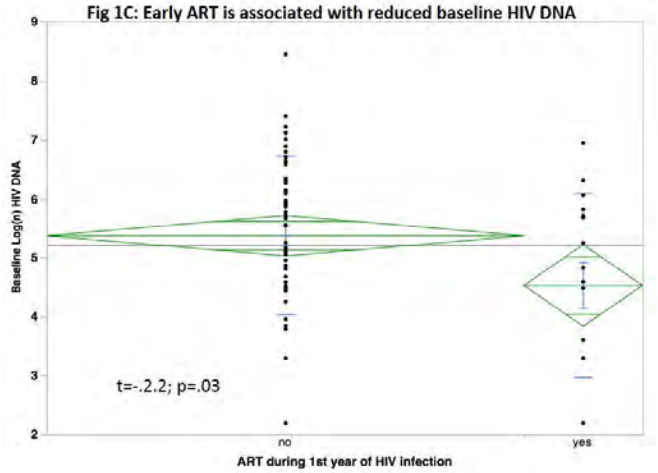
Background: The HIV reservoir in peripheral blood mononuclear cells (PBMC) contributes to HIV-associated dementia (HAD) pathogenesis. However it is unclear whether it contributes to non-demented HIV-associated neurocognitive disorders (HAND) that are more common in chronic HIV infection (CHI), especially in HIV+ persons on long-term combined antiretroviral therapy (cART).

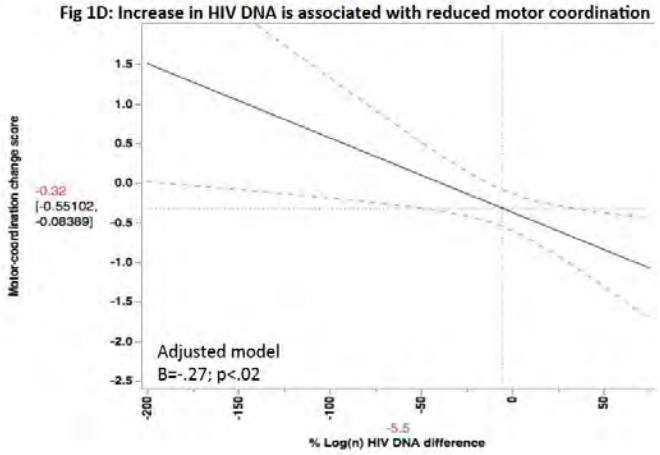
Methods: Eighty adults (mean age=55, 1 female) with CHI on cART (>97% with undetectable plasma and CSF HIV RNA) underwent assessments of neurocognition and pre-morbid cognitive ability (Australian standardized index of education and reading) at two visits 18 months apart. HIV DNA in PBMC was measured by real-time PCR at the same time-points. Historical HIV disease data included: duration of HIV infection (median=19 years); ART during 1st year of HIV infection (20%); current (556) and nadir (194) median CD4 count; none developed AIDS during study.

Results: At baseline, 46% of the patients had non-demented HAND; 7.5% had HAD. At follow-up, neurocognitive function declined in 14%, and this was more likely in those with baseline HAD (p<.03). Low pre-morbid cognitive ability was uniquely associated with HAD (p<.05). Log(n) HIV DNA copies were stable between study visits (5.2 vs. 5.1 per 10^6 PBMC; r=.73). Univariate analyses showed that baseline HIV DNA was *higher* in those with *longer* duration of infection (r=.28; p<.02, Fig.1B) as well as those with *lower* pre-morbid cognitive ability (r=-.24; p<.04, Fig.1A) and was higher in those with no treatment during HIV infection 1st year (5.4 vs. 4.5; p=.03, Fig.1C). Multiple regression models showed that baseline HIV DNA was not associated with baseline overall neurocognitive performance in unadjusted and adjusted (above significant factors plus CD4 count, age, cART duration) models. Change in HIV DNA between study time-points was associated with a decline in motor-coordination, r=-26, p<.03 (Fig.1D); and semantic fluency, r=-25, p<.03; and this remained significant in adjusted models (p<.02).









Conclusions: PBMC HIV DNA was not associated with current non-demented HAND, but an increase in HIV DNA during the study period was associated with decline in some neurocognitive functions. Further, the role of PBMC HIV DNA in HAD pathogenesis is moderated by pre-morbid cognitive. Lastly, higher baseline HIV DNA was associated with longer duration of HIV disease. Further study is needed to investigate if these results are reproduced when focusing on HIV DNA in monocytes.

438 Acute HIV CSF/Plasma RNA Ratios Are Variable and Greater Than in Chronic HIV

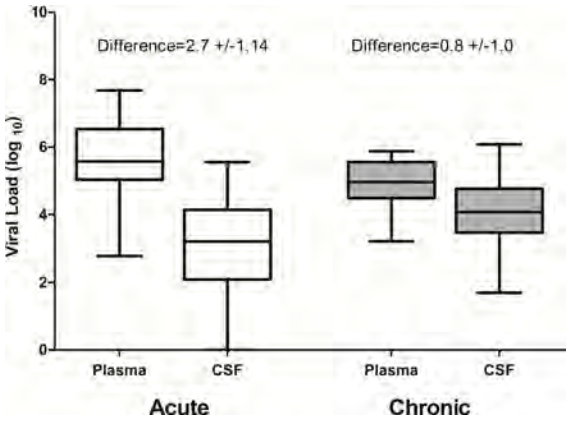
Joanna Hellmuth[1]; Serena Spudich[2]; Eugene Kroon[3]; Naponpon Sailasuta[4]; Somprartthana Rattanamanee[3]; Sukalaya Lerdlum[5]; Linda L. Jagodzinski[6]; Shelly J. Krebs[7]; Jintanat Ananworanich[8]; **Victor G. Valcour**[1]
The RV254/SEARCH010 Study Group

[1]University of California San Francisco, San Francisco, CA, US; [2]Yale University School of Medicine, New Haven, CT, US; [3]Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [4]University of Hawaii, Honolulu, HI, US; [5]Chulalongkorn University, Bangkok, Thailand; [6]Walter Reed Army Institute of Research, Silver Spring, MD, US; [7]Henry M. Jackson Foundation for the Advancement of Military Medicine, Silver Spring, MD, US; [8]US Military HIV Research Program, Bethesda, MD, US

Background: Clarifying the early dynamics of HIV invasion into the central nervous system (CNS) will inform understanding of the neurologic complications of HIV, and may facilitate cure interventions that rely on preventing establishment of viral reservoirs.

Methods: Forty-two Thai subjects identified in the acute phase of HIV infection (Fiebig I-V) had plasma and cerebrospinal fluid (CSF) samples for viral load and cytokine analysis, and magnetic resonance spectroscopy (MRS) an average of 16 days after self-reported estimated date of infection and all with measurable HIV RNA in plasma. We examined factors associated with ultra-low CSF HIV RNA (unquantifiable or undetected) compared to those with measurable CSF HIV RNA and examined the mean difference between log_{10} plasma and CSF HIV RNA during acute HIV infection (AHI). Pre-cART plasma and CSF viral loads were compared to that of 42 Thai cases evaluated just prior to cART initiation during chronic HIV.

Results: AHI subjects (n=42) were mean age of 29.8 (+/-7.8) and 9.5% female, whereas the 42 chronic cases were mean age of 34 (+/-6.6) and 54.8% female. 50% of chronic cases had a diagnosis of HIV-associated neurocognitive disorder (HAND). The mean difference between log_{10} plasma and CSF HIV RNA was 2.7 +/-1.4 for AHI compared to 0.8 +/-1.0 for chronic cases ($p<0.0001$). Ten of 42 AHI subjects had unquantifiable CSF HIV RNA and these cases tended towards the earliest stages of infection: Fiebig I (n=8); II (n=1); III (n=1). Individuals with undetectable CNS HIV RNA were then one-to-one matched by Fiebig stage to a random selection of cases with quantifiable CSF HIV RNA. Cases with unquantifiable CNS HIV RNA showed lower serum neopterin ($p<0.05$) and trended toward lower log_{10} CSF IP-10 ($p<0.08$).



Conclusions: The difference between log10 plasma and CSF HIV RNA (ratio of plasma/CSF) is significantly higher in acute compared to chronic HIV infection, with some individuals in the earliest stages of AHI manifesting ultra-low levels of HIV RNA in CSF. Subjects with initially ultra-low CSF HIV RNA trend towards lower markers of monocyte activation.

439 Greater CSF HIV Reduction and CSF Rapid Decay Associated with Improved Neurocognition

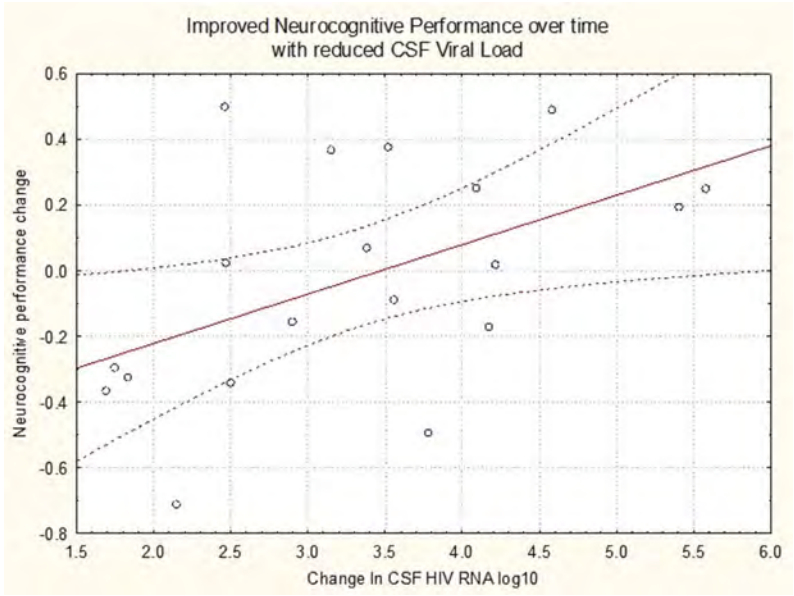
Kevin R. Robertson[1]; Natalie M. Bowman[1]; Sarah B. Joseph[1]; Prema Menezes[1]; Nisha Bhatia[2]; Christopher Lippincott[1]; Michael Vinikoor[1]; Joseph Eron[1]; Ronald Swanstrom[1]; Richard Price[2]
THINC UNC

[1]*University of North Carolina, Chapel Hill, Chapel Hill, NC, US;* [2]*University of California San Francisco, San Francisco, CA, US*

Background: HIV Associated Neurocognitive impairment remains problematic despite suppressive antiretroviral therapy (ART). Underlying low level HIV infection likely persists in the central nervous system (CNS) and may sustain inflammation causing neuronal damage. We sought to better understand the dynamics of HIV in the cerebrospinal fluid (CSF) during treatment initiation and the relationship to neurocognitive outcomes.

Methods: In THINC (the HIV Tropism, Persistence, Inflammation and Neurocognition in Therapy Initiation cohort) treatment-naïve patients initiating ART with CD4 < 400 were administered neurocognitive testing and lumbar puncture (LP) at baseline. A follow-up LP was performed after 2-4 weeks on ART, and a neurocognitive follow-up was performed after 24 weeks on ART. The neurocognitive battery assessed Premorbid/language, Fluency, Executive, Learning, Memory, Speed of Processing, and Fine motor domains. We correlated change in total z score with overall change in log CSF HIV RNA, and decay as measured by change in CSF HIV RNA divided by days on ART to estimate the association of neurocognitive performance with CSF viral load and CSF decay.

Results: Of 38 patients who underwent baseline neurocognitive testing and LP, 30 also received the follow-up LP and 27 also received the follow-up neurocognitive assessment. The total z score across the neurocognitive battery at baseline had a mean of -0.91 (range -2.7 to 0.49; SD 0.66), and the mean change (computed from follow up minus baseline so that positive scores reflect improvement) was .06 (range -0.71 to 1.16; SD 0.39). The baseline log CSF HIV RNA median was 3.14 (n=38, range 1.04 to 5.58; SD 1.06), and the median change (positive numbers reflect improvement) was 3.27 (n=26, range 1.69 to 5.58; SD 1.04). There was a significant correlation between greater reduction in CSF HIV RNA and total z score change (r= .51, p<.05; see graph). CSF decay rate % was significantly associated with total z score change (r=.53, p<.05). However, no significant correlations with *baseline* total z score were found with baseline CSF HIV RNA, change in CSF VL, or CSF decay.



Conclusions: A greater reduction and more rapid decay of CSF HIV after ART initiation was related to greater improvement in neurocognitive functioning after initiating ART. Reduced viral load in the CNS likely reduces ongoing inflammatory processes causing injury to neurons, resulting in relatively improved neurocognition.

440 HIV-1 Replication in the CNS Is Associated With Increased Neurocognitive Impairment

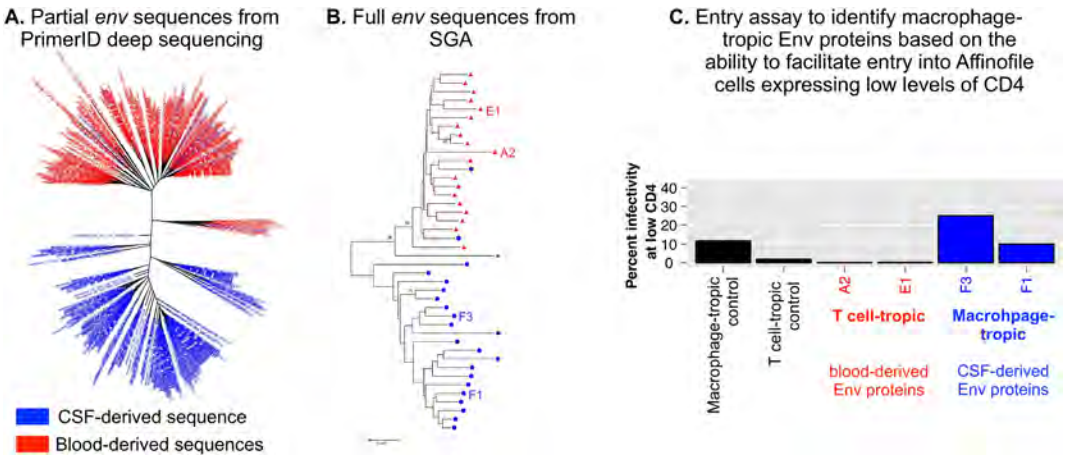
Sarah B. Joseph[1]; Laura Kincer[1]; Natalie M. Bowman[1]; Prema Menezes[1]; Kevin Robertson[1]; Albert M. Anderson[2]; David W. Loring[3]; Joseph J. Eron[1]; Richard W. Price[4]; Ronald Swanstrom[1]

[1]University of North Carolina, Chapel Hill, Chapel Hill, NC, US; [2]Emory University, Atlanta, GA, US; [3]Emory University, Atlanta, GA, US; [4]University of California San Francisco, San Francisco, CA, US; [5]University of North Carolina, Chapel Hill, Chapel Hill,, NC, US

Background: HIV-infected individuals are reported to have higher levels of neurocognitive impairment than HIV-negative controls. We examined the association between independent HIV-1 replication in the CNS and neurocognitive impairment.

Methods: We used cerebrospinal fluid (CSF) and blood plasma samples from 40 subjects off antiretroviral therapy (ART) to characterize viral populations in the CNS and blood. Subjects were enrolled in 1 of 4 cohorts. Two cohorts enrolled subjects based on neurological symptoms and two enrolled subjects based on CD4 count and viral load. All subjects had neurocognitive assessments. cDNA was generated from viral RNA and partial *env* genes were amplified and sequenced by Illumina deep sequencing with Primer ID to quantify the number of templates examined (Fig. 1A); and/or full length *env* genes were amplified and sequenced by single genome amplification (SGA)(Fig. 1B). Pseudotyped viruses were generated from cloned, full-length *env* genes and used in entry assays to determine whether Env proteins were well-adapted to entering cells expressing low levels of CD4 (i.e. macrophage-tropic; Fig 1C).

Results: Based on formal neurocognitive assessments, subjects were classified into three groups with increasing levels of neurocognitive impairment: 1) normal (N=7), 2) mild neurocognitive disorder or asymptomatic neurocognitive impairment (N=10), and 3) HIV-associated dementia (N=23). The observation of genetically distinct, viral lineages in the CSF was evidence of ongoing replication in that compartment, and these lineages were considered compartmentalized (Fig. 1A and 1B). Increasing neurocognitive impairment was positively associated with compartmentalization (exact trend test, p=0.04). For 71% of subjects with compartmentalized HIV-1 in their CSF, this virus was also macrophage-tropic, and thus compartmentalization was significantly associated with macrophage tropism (fisher's exact test, p= 0.001).



Conclusions: HIV-1 replication in the CNS is strongly associated with neurocognitive impairment and the majority of subjects with evidence of ongoing HIV-1 replication in the CNS have macrophage-tropic HIV-1 in that compartment. These results suggest that there may be a causal relationship between HIV-1 replication in macrophage-lineage cells in the CNS and neurocognitive symptoms in HIV-infected subjects off therapy. Antiretroviral therapy that fully suppresses viral replication in the CNS, particularly in macrophages, may be more likely to improve neurocognitive performance.

TUESDAY, FEBRUARY 24, 2015

Session P-G2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Optimizing ART for HAND Treatment and Prevention

441 Maraviroc-Enhanced CART Improves Cognition in Virally Suppressed HAND: A Pilot Study

Thomas M. Gates[1]; Lucette A. Cysique[2]; Joga Chaganti[1]; Krista J. Siefried[1]; **Bruce J. Brew**[1]

[1]St Vincent's Hospital, Sydney, Sydney, Australia; [2]Neuroscience Research Australia (NeuRA), Sydney, Australia

Background: HIV-associated neurocognitive disorders (HAND) occur despite viral suppression in blood and cerebrospinal fluid on combined antiretroviral therapy (CART). One therapeutic option may be CART enhancement with Maraviroc (MA) as MA can penetrate the Central Nervous System (CNS) and has dual antiretroviral/anti-inflammatory activity.

Methods: 19 virally-suppressed HIV+ males (M=53 years old) with formally diagnosed HAND were enrolled in a prospective, randomized, double observer-blinded, open-label pilot RCT. Two subjects failed screening. One subject withdrew for personal issues, 2 were lost to follow-up. Of 14 subjects completing all study visits, 9 were randomized to receive MA enhancement and 5 to continue on existing CART. 2 MA and 1 control subject had confirmed CXCR4-tropic virus in blood; 1 control had confirmed CCR5-tropic virus. HIV tropism status was unavailable for other subjects. Subjects completed neurocognitive (NR) testing assessing 5 cognitive domains at baseline, 6- and 12-months. Primary endpoint was NR change across study period (defined as a global z-score averaging each domain z-score correcting for age and gender). Secondary endpoints were ^{1}H-MR Spectroscopy (MRS) metabolite concentrations in the basal ganglia (BG) and frontal white matter (FWM) at Baseline and 12-months and quantified using LC Model. NR change was analyzed using mixed effect linear regression models with fixed effects: arm, time, arm*time interaction and subject as a random effect to account for attrition. In total, 38 subject visits were included in the analyses (MA: n=27; control: n=14). MRS change was analyzed using repeated measures ANOVA with same fixed effects. Trends p<.10 are reported as this represents pilot data in a small sample. Effect sizes Cohen's d and β assist in interpretation of effect.

Results: A trend was found for arm*time interaction (p=.056), with 6-month effect size d=1.2 and 12-month effect size d=.45, in favour of improved NR performance in MA arm compared to control arm over time (Figure 1). BG glutamate concentration (a marker of excitotoxicity) was stable in MA arm but tended to increase in control arm at 12 months (interaction: p<.08; β=.-35).

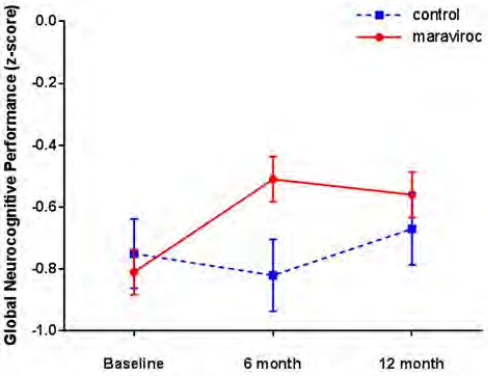


Figure 1. Mean (±SD) global neurocognitive performance over time based on model adjusted least mean squares (treatment arm*time interaction $p=.056$).

Conclusions: This pilot study provides feasibility, tolerability, proof-of-concept and preliminary evidence for clinically significant neurocognitive improvement and potential stabilization of glutamate excitotoxicity in CART enhancement with MA in virally suppressed HAND patients.

442 Similar Neurocognitive Performance in Patients on ATV/r Monotherapy vs Triple Therapy

Giada Caramatti[1]; Francesca Ferretti[1]; Antonio Di Biagio[2]; Amedeo Capetti[3]; Andrea Antinori[4]; Fiorella Di Sora[5]; Roberta Gagliardini[6]; Concetta Vinci[1]; Adriano Lazzarin[1]; **Laura Galli**[1]

[1]San Raffaele Scientific Institute, Milan, Italy; [2]Azienda Ospedaliera San Martino, Genoa, Italy; [3]L. Sacco University Hospital, Milan, Italy; [4]National Institute for Infectious Diseases IRCCS Lazzaro Spallanzani, Rome, Italy; [5]Ospedale San Giovanni, Rome, Italy; [6]Catholic University of the Sacred Heart, Rome, Italy

Background: To assess efficacy in Central Nervous System (CNS), we evaluated neurocognitive performance in patients (pts) on atazanavir/ritonavir (ATV/r) monotherapy compared to ATV/r triple therapy.

Methods: MODAt (NCT01511809) is a multicentric, randomized, open-label, non-inferiority trial. Pts on ATV/r 300/100mg+2 N(t)RTIs since≥48 weeks, virologically suppressed since≥24 weeks, were randomized to ATV/r (arm A) or to maintain ATV/r+2N(t)RTIs (Arm B). This analysis included patients treated with either ATV/r triple therapy or monotherapy (with no re-intensification due to virological failure) who underwent neuropsychological (NP) evaluation at baseline, week 48 and, if not discontinued, at week 96. The NP tests assessed multiple cognitive domains including attention/concentration (Digit Symbol [DS]), learning/memory (Rey Auditory Verbal Learning Test [RAVLT], Rey Recall [RAVLT rec]); psychomotor speed (Trail Making Test–Part A [TMTA], Grooved Pegboard [GP]), executive functioning (TMT–Part B [TMTB]), language (Semantic [SF] and Phonemic fluency [PF]), and gross motor (finger tapping [FT]). Age, sex and education adjusted scores were used. Depression was assessed using the CES-D scale. Results are expressed as median (interquartile range). ANOVA for repeated measures and McNemar test were applied for longitudinal analysis.

Results: Sixty-five pts were examined (Arm A=28, Arm B=37): 88% males; age, 40 (35-46) years; education, 13 (12-15) years; duration of HIV-infection, 5 (2-7) years; CD4+ nadir, 293 (224-388) cells/μL; baseline CD4+, 610 (431-774) cells/μL, pre-ART HIV-RNA 4.67 (4-5.26) log10cp/mL; HCV co-infection (15%); none with AIDS diagnosis. Baseline NP findings were similar between the two arms with the exception of TMT-B scores that were worse in arm B compared to arm A (p=0.018). At baseline, CES-D score was abnormal (score>23) in 11 (17%) pts, borderline (score: 17-23) in 10 (15%) pts, with no significant changes of these proportions during follow-up. NP scores improved significantly over 96 weeks in five of nine tests [Figure] with no trend differences between arms. The proportion of pts with HIV-Associated Neurocognitive Disorders (HAND) dropped from 66% at baseline to 37% at week 96 with no differences between arms.

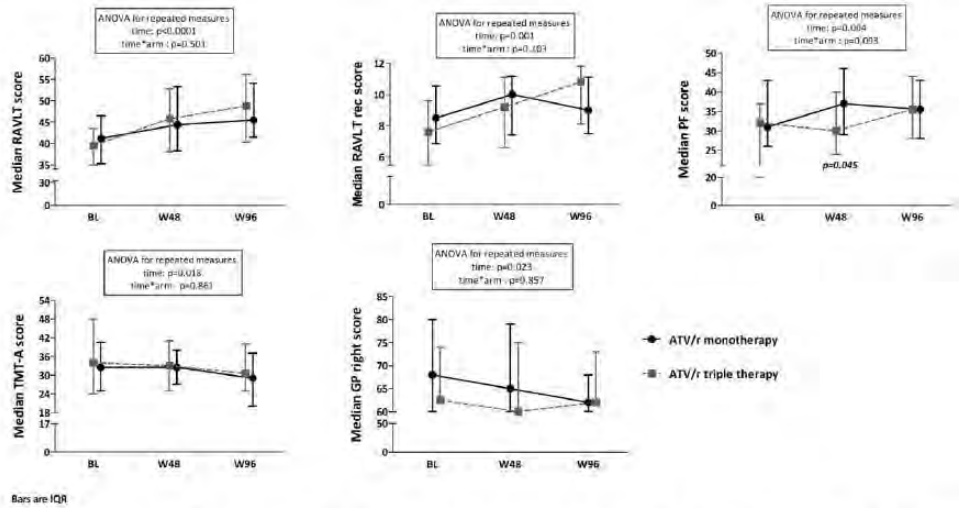


Figure. Neuropsychological test with significant improvement over 96 weeks according to study arm.

Conclusions: In subjects successfully treated for 96 weeks, we observed an improvement in the majority of explored NP test performances with similar trends in patients treated with ATV/r-monotherapy or ATV/r triple therapy.

443 Cerebrospinal Fluid Markers in Long-Term Atazanavir/Ritonavir Monotherapy

Francesca Ferretti; Alba Bigoloni; Valeria Longo; Laura Galli; Laura Passeri; Simonetta Gerevini; Vincenzo Spagnuolo; Adriano Lazzarin; Paola Cinque; Antonella Castagna
San Raffaele Scientific Institute, Milan, Italy

Background: Central nervous system (CNS) viral escape is a concern in ritonavir boosted protease inhibitors monotherapy. Aim was to assess viral escape and immuneactivation marker levels in the cerebrospinal fluid (CSF) of patients on successful long-term atazanavir/ritonavir (ATV/r) monotherapy.

Methods: MODAt (NCT01511809) is a multicentric, randomized, open-label, non-inferiority trial. Patients on ATV/r 300/100mg+2 N(t)RTIs since≥48 weeks, virologically suppressed since≥24 weeks, were randomized to ATV/r-monotherapy (arm A) or to maintain ATV/r+2N(t)RTIs (arm B). In this sub-study, paired CSF and plasma samples were collected in patients with plasma HIV-RNA viral load <50 c/mL at ≥96 study weeks, including those with early re-intensification for confirmed viral failure, considered in arm B, after evaluation with brain magnetic resonance imaging (MRI) to assess HIV-RNA and immuneactivation markers soluble CD14 (sCD14) and CD163 (sCD163), CCL2, CXCL10 and interleukin-6 (IL-6) by ELISA. Results are expressed as median (interquartile range). Variables were compared with Wilcoxon rank sum or Fisher exact test, as appropriate; Spearman test was applied to assess correlations.

Results: We evaluated 23 patients (Arm A=11, Arm B=12): 95% males, 43 years old (38-47), with nadir CD4+ cells 334/μL (268-366), pre-treatment HIV-RNA 4.86 log10 c/mL (4.49-5.43), no previous AIDS diagnosis, CD4+ at randomization of 599 cells/μL (467-699) and undetectable plasma VL since 19.5 months (13.7-48.7). At CSF evaluation, after 120 (108-132) weeks, all patients were neuroasymptomatic, had no pathological MRI findings and CD4+ 679 (443-925) cells/μL (similar between the two arms, p=0.705). CSF HIV-RNA was detected in no patients on triple therapy and in one on monotherapy (study week 120, nadir CD4+ of 311 cells/μL, two HIV-RNA blips of 94 and 99 c/mL during the study), who was re-intensified.

CSF biomarker levels did not differ between the two arms. CSF cell number (normal range ≤1 cell/μL) was slightly higher in the monotherapy arm (Table). Overall, CSF IL-6 was significantly correlated with plasma IL-6 (r=0.70, p<0.001) and CSF sCD14 with plasma sCD14 (r=0.49, p=0.016).

	ATV/r-monotherapy (n=11)	ATV/r+2N(t)RTIs (n=12)	p
CSF HIV-RNA >50c/mL	1 (114 c/mL)	0	-
CSF Cells/μL	2 (1-4)	1 (1-1)	0.034
CSF sCD14 (ng/mL)	97 (16-162)	58 (0.1-199)	0.502
Plasma sCD14 (ng/mL)	2165 (1755-2815)	1735 (1245-2051)	0.047
sCD163 (ng/mL)	34.7 (23.0-51.4)	27.1 (17.5-51.4)	0.682
CSF CCL2 (pg/mL)	314 (108-708)	302 (154-526)	0.549
Plasma CCL2 (pg/mL)	112 (1.6-135)	1.6 (1.6-102)	0.230
CSF IL-6 (pg/mL)	3.76 (2.28-6.39)	2.80 (2.15-3.44)	0.377
Plasma IL-6 (pg/mL)	2.86 (1.51-4.97)	1.51 (1.13-2.15)	0.063
CSF CXCL10 (pg/mL)	123 (35-257)	66 (26-139)	0.394
Plasma CXCL10 (pg/mL)	123 (79-164)	87 (59-117)	0.101

Conclusions: CSF escape was uncommon in asymptomatic patients on long-term, successful ATV/r monotherapy. CSF immune activation was not substantially different between patients on ATV/r monotherapy compared to triple therapy.

444 Neurocognitive Decline Is Associated With Antiretroviral Concentrations in Plasma and Cerebrospinal Fluid (CSF)

Qing Ma[1]; Xia Liu[2]; Robert Heaton[1]; Fujie Zhang[2]; Hua Jin[1]; Hao Wu[2]; Melanie Crescini[1]; Hongxin Zhao[2]; Hui Zeng[2]; Scott Letendre[1]
[1]University of California San Diego, San Diego, CA, US; [2]Chinese Center for Disease Control and Prevention, Beijing, China

Background: Therapeutic antiretroviral therapy (ART) drug concentrations in the central nervous system (CNS) are likely important for controlling HIV replication in the brain although their relationship to neurocognitive impairment (NCI) remains controversial. The objective was to investigate associations between drug concentrations with incident NCI in a randomized clinical trial comparing two ART regimens, tenofovir-lamivudine-efavirenz (TDF-3TC-EFV, T3E) and zidovudine-lamivudine-nevirapine (ZDV-3TC-NVP, Z3N), in China.

Methods: A total of 23 HIV+ adults were evaluated in a nested case-control substudy: 11 who developed NCI (decliners) after 48 weeks of ART and 12 who did not (non-decliners). Cases and controls were matched by sex, education, ethnicity, and baseline NC performance, but not treatment regimen. Plasma and CSF were sampled at a median of 12.4 hours post-dose and drug concentrations were measured by LC/MS/MS.

Results: Subjects were all Han Chinese men with a mean age of 32.9 years. All subjects had plasma HIV RNA levels below 50 c/mL. Similar to the findings of the parent trial (presented in a separate abstract), decliners were more frequently randomized to T3E (58.3% vs. 36.4%, RR 1.53). Decliners had markedly higher plasma TDF concentrations (d=2.2, p=0.004) and lower TDF CSF-to-Plasma Ratios (CPRs, d=1.3, p=0.028) than non-decliners with a trend towards higher EFV CPRs (d=1.0, p=0.09). Recursive partitioning identified that none of the 5 subjects who had plasma TDF concentrations < 33.5 ng/mL were decliners while all 6 subjects who had plasma TDF concentrations ≥ 33.5 ng/mL and EFV CPRs ≥ 0.46% were (p=0.0004).

Conclusions: In this small, nested case-control study, incident NCI was associated with TDF and EFV drug concentrations. The observed association with low TDF CPRs may reflect suboptimal antiviral efficacy in the CNS while the association with high EFV CPRs may reflect neurotoxicity. Together, the observed CPR associations may indicate disturbances in the permeability and drug transport properties of the blood-brain barrier that predispose to development of HIV-associated NCI.

445 Viral Decay Rate in the Cerebrospinal Fluid After Initiating Antiretroviral Therapy

Natalie M. Bowman[1]; Sarah B. Joseph; Prema Menezes[1]; Jessica Margolis[1]; Christopher Lippincott[1]; Michael J. Vinikoor[1]; Kevin R. Robertson[1]; Richard Price[2]; Ronald Swanstrom[1]; Joseph Eron[1]
[1]University of North Carolina, Chapel Hill, NC, US; [2]University of California San Francisco (UCSF), San Francisco, CA, US

Background: Initiation of antiretroviral therapy (ART) typically results in the rapid decay of HIV-1 in the cerebrospinal fluid (CSF); however, in a subset of HIV-infected people, virus in the CSF decays very slowly despite the use of ART. We examined factors that predict the rate of viral decay in the CSF after initiating ART.

Methods: We recruited treatment-naïve patients with CD4 < 400 starting antiretroviral therapy (ART). All participants underwent medical and neurological examination, neuropsychiatric testing, blood draw, and lumbar puncture (LP) at baseline and 2-4 weeks after initiation of ART. We measured blood and CSF HIV viral loads (VL), CD4 count, and

blood and CSF laboratories at each visit. VLs less than 40 were estimated as 20 if undetectable and as the exact copy number when detectable. Decay rates were calculated as change in log(VL) divided by number of days on ART. Multivariate linear regression was used to identify predictors of CSF VL decay rates.

Results: 40 treatment-naïve patients (35 men, 5 women) underwent baseline LP and 30 returned for LP 2 weeks after initiation of ART. Median CD4 count was 259 (range 6-424). Median blood HIV VL was 42,269 copies/mm^3 (168-2,184,166) at baseline and declined to 205 (<40-26,417) at week 2. At baseline, 98% of subjects had detectable CSF HIV VL (median 1197, range 11-381,030); at 2 weeks 77% had detectable CSF HIV, and mean log(CSF VL) declined by 1.24. In bivariate analyses, log(CSF VL) at baseline and 2 weeks were correlated (p=0.0002) and log(CSF VL) and log(blood VL) at 2 weeks were correlated (p=0.003). Log-linear CSF VL decay rates were correlated with baseline CSF VL (p=0.0001) and with baseline CSF white blood cell count (p=0.03); there was a non-significant trend towards correlation with blood VL at baseline (p=0.1). Protease inhibitor use was associated with faster CSF viral decay (p=0.04) while integrase inhibitor use was associated with non-significantly slower decay, though this relationship did not hold for blood VL. Multivariate analyses (N=28) of predictors of CSF VL decay are shown in the table.

	Log-linear decay rate	
Variable	Change in rate per 1-unit change in log decay rate or log(CSF VL)	95% confidence interval
log(blood VL decay rate)	1.40	1.11-1.77
log(baseline CSF VL)	1.04	1.02-1.05

Conclusions: Baseline higher CSF VLs and faster blood VL decay rates predicted faster decay of HIV in CSF after initiation of ART. Though not significant in multivariate analyses, PIs were associated with faster CSF viral suppression while integrase inhibitors were associated with slower suppression, findings which may have implications for ART choice in patients with HIV-associated neurocognitive findings.

446 Rates of Nonconfounded HIV-Associated Neurocognitive Disorder After Early cART

Teresa H. Evering[1]; Allison Applebaum[2]; Melissa La Mar[1]; Donald Garmon[1]; David Dorfman[3]; Martin Markowitz[1]

[1]Aaron Diamond AIDS Research Center, an Affiliate of the Rockefeller University, New York, NY, US; [2]Memorial Sloan-Kettering Cancer Center, New York, NY, US; [3]Mount Sinai School of Medicine, New York, NY, US

Background: HIV-Associated Neurocognitive Disorder (HAND) is an important complication of chronic HIV-infection with an estimated prevalence ranging from 19 - 45%. We investigated the prevalence of non-confounded HAND in an HIV positive cohort who previously initiated long-term cART with a median duration of infection of 1.6 months.

Methods: Participants were randomly selected from the ADARC Primary HIV-1 Infection Cohort. Exclusion criteria included: treatment interruption since cART initiation, severe neuropsychiatric disorder, active major depressive disorder, DSM-IV diagnostic criteria for alcohol/substance abuse or dependence within 1 year prior to screen (excluding marijuana), untreated syphilis and positive hepatitis C serology. The Beck Depression Inventory (BDI) was used to determine severity of depressive symptoms. We assessed neurocognitive (NC) function comprehensively and those with global deficit scores (GDS) $\geq$0.50 were considered impaired. Associations between GDS scores and clinical parameters were evaluated using multiple linear regression.

Results: Forty individuals screened and a high screen failure (SF) rate (14/40 = 35%) was observed. The most common reasons for SF were active methamphetamine/other substance dependence (5/14 = 36%) and active bipolar disorder (3/14 = 21%). Twenty-six, primarily non-Hispanic white (73%), male (100%) subjects were enrolled and underwent NC assessment. Mean age was 43 (28-71) years, with a median of 17 years of education (13-24). Median current and nadir plasma CD4+ T cell counts were 828 (506-1411) and 359 (150-621) cells/μL. Median duration of cART prior to enrollment was 5.7 years (2.2-9.9). Median 2010 CPE score at study entry was 7 (6-10) and all participants had plasma HIV-1 RNA <50 copies/ml at this time. Median BDI score was 1 (0-13). Median GDS was 0.17 (0.00-0.50). Only 1 (4%) participant was impaired. There was no association between GDS and any clinical/immunologic parameter ($p \geq 0.27$, all variables). Individuals failing screening were demographically similar to those enrolled.

Conclusions: Observed rates of HAND in this cohort of HIV-infected individuals without confounding comorbidities that initiated cART during acute/early infection are low. Our findings suggest substantial neuroprotective benefit of initiating cART during primary infection, but also highlight the pervasiveness of comorbid illness in those with HIV and suggest a significant contribution of comorbidities to observed HAND prevalence.

447 The Impact of HAART CNS Penetration Effectiveness on Brain Integrity in HIV+ Adults

Laurie Baker[1]; Robert H. Paul[1]; Jodi M. Heaps[1]; Mario Ortega[2]; Christin Usher[1]; Jee Yoon Chang[2]; Beau Ances[2]

[1]University of Missouri St Louis, St Louis, MO, US; [2]Washington University School of Medicine, St Louis, MO, US

Background: Highly active antiretroviral therapy (HAART) reduces morbidity and mortality due to human immunodeficiency virus (HIV), however cognitive impairment continues to persist. It remains uncertain whether HAART regimens with a high degree of central nervous system penetration effectiveness (CPE) exert beneficial neurological outcomes in HIV-infected (HIV+) individuals on stable treatment. The present cross sectional study examined the relationship between HAART CPE and brain integrity in HIV+ adults.

Methods: Sixty-four HIV-infected individuals (18-82 years old) on stable HAART (≥ 3 months) were assigned a CPE score using a published ranking system and divided into high (≥ 7; n=35) and low (< 7; n=29) CPE groups. All participants completed laboratory and neuropsychological testing in addition to structural neuroimaging. Neuropsychological tests included measures known to be sensitive to HIV with values converted into standardized scores (NPZ-4) based on published normative scores. A semi-automated methodology was utilized to assess brain volumetrics within cortical (white and grey matter) and subcortical (caudate, putamen, and thalamus) regions of interest often affected by HIV. Primary analyses utilizing linear regression were computed to examine the relationship between total CPE score with NPZ-4 and brain volumetrics. Differences in demographic (age, education, race, gender) and viral factors (recent viral load, duration of infection, recent CD4, CD4 nadir) between high (≥ 7) and low (< 7) CPE groups were examined utilizing independent sample t tests and chi-squared analyses. Secondary analyses utilized analysis of variance to assess NPZ-4 and brain volumetric differences between HIV+ individuals with high and low CPE scores.

Results: Primary analyses revealed no significant relationships between neuropsychological performance ($F(1,63)=1.01$; $p > .05$) or brain volumetrics ($F(5,67)= .27$, $p > .05$) and total CPE score utilizing linear regression. There were no differences in demographic or viral factors between the two CPE groups. Furthermore, no significant relationships were observed in the secondary analyses when individuals were categorically divided into high or low CPE groups ($p > .05$).

Conclusions: Long-term HAART regimens with a high degree of CPE were not associated with significantly improved neuropsychological or neuroimaging outcomes in HIV+ adults. Results suggest that alternate mechanisms may potentially contribute to better neurological outcomes in the era of HAART.

448 Efavirenz Use is Not Associated with Increased Risk of Neuropsychological Impairment

Sean B. Rourke[1]; John Gill[2]; Anita Rachlis[1]; Colin Kovacs[4]; Gordon Arbess[5]; Jason Brunetta[4]; Adriana Carvalhal[1]; Chris Power[2]; Ann N. Burchell[3]; Tsegaye Bekele[3]

[1]University of Toronto, Toronto, Canada; [2]University of Alberta, Calgary, Canada; [3]The Ontario HIV Treatment Network, Toronto, Canada; [4]Maple Leaf Medical Clinic, Toronto, Canada; [5]St. Michael's Hospital, Toronto, Canada

Background: Efavirenz is known to increase neuropsychiatric symptoms shortly after initiation of therapy, and while these generally resolve within 2-3 months, the evidence on whether there is an increased risk of neuropsychological impairment (NPI) which persist is mixed. The purpose of this study is to examine whether people living with HIV who are on cART that includes Efavirenz have higher risk of NPI.

Methods: Study participants were HIV patients on cART from two outpatient clinics in Toronto, Canada. Neuropsychological assessment was done every 12 months (median follow-up time: 24.5 months) using a brief test battery that included Hopkins Verbal Learning Test- Revised (HVLT-R), Grooved Pegboard, and WAIS-R Digit Symbol tests. Demographically corrected T-scores and Global Deficit Score were computed. NPI was defined using a Global Deficit Score of 0.5 or greater. We estimated the odds of NPI using Generalized Estimating Equations adjusting for baseline and time-dependent covariates.

Results: 831 adults (80% men, 62% Caucasian, 84% with undetectable HIV viral load) with 2,160 observations were included. Nearly one-third (n=266, 32%) were on Efavirenz, 234 (28%) had used Efavirenz in the past, and 331 (40%) were Efavirenz naïve. Prevalence of NPI was slightly higher among those who were Efvairenz naïve (63%) than those who had been on Efavirenz in the past (57%) or those who are on Efavirenz currently (56%) at baseline. In unadjusted logistic regression analysis, current Efavirenz use was associated with significantly lower odds of NPI (OR=0.72; 95% CI: 0.53-0.97; p=0.033), while past use of Efavirenz showed no association (OR=0.76; 95% CI: 0.56-1.03, p=0.079). In multivariate logistic regression, however, the association between current Efavirenz use and NPI was no longer significant (OR= 0.77; 95% CI: 0.57 to 1.05; p=0.099). Among the covariates examined, nadir CD4 count <200 cells/mm^3(OR=1.40; 95% CI: 1.047-1.84; p=0.016), Hepatitis C infection (OR= 1.58; 95% CI: 1.06-2.35; p=0.002), and diabetes (OR=2.32, 95% CI: 1.30-4.16; p=0.005) were associated with higher odds of NPI.

Conclusions: Current or past use of Efavirenz is not associated with an increased risk of neuropsychological impairment in our Ontario sample which replicates the findings of Antinori et al (2014) in a Canadian sample.

449 Quantitative Electroencephalogram as a Translational Biomarker for NNRTI CNS AEs

Pamela Tannenbaum; Jacquelyn Binns; Spencer Tye; Alan Savitz; Steven Fox; Christopher Burgey; Ming-tain Lai; Arthur Simen; daria hazuda; **Michael D. Miller**

Merck and Co, Inc, West Point, PA, US

Background: Although it is an effective drug for treating HIV-1 infection, the non-nucleoside RT inhibitor (NNRTI) efavirenz (EFV) elicits significant CNS adverse events (AEs) such as insomnia, headache, nausea, dizziness, cognitive impairment and depression. Currently marketed NNRTIs vary in efficacy and have varying degrees of CNS AEs. Therefore, an NNRTI with high efficacy and low potential for CNS toxicities is still needed to maximize the utility of the class.

Methods: Freely-moving rats (n=16) and monkeys (n=12) were implanted with telemeterized EEG, electromyography and electrooculogram transmitters and recorded 24hr/day. In a within-subjects cross over design, animals were dosed with 50-200mg/kg EFV (BID, PO) or vehicle for 14 days each. Recordings were analyzed for sleep/wake and qEEG spectral frequency changes. Spectral differences were also compared to our EEG data collected previously on healthy volunteers receiving EFV (600mg QD) with cognitive impairment (Simen et al, J Sleep Res 2014).

Results: In both rats and monkeys, EFV produced sedation and a significant dose-responsive qEEG signature of increased low-frequency bands (Theta-Alpha) with decreased mid-frequency bands (Sigma-Beta). This signal appeared within 1-2 days of initial exposure and diminished across the first week of treatment. Our previous healthy volunteer EFV EEG study produced a strikingly similar increase in Theta-Alpha plus decrease in Sigma-Beta qEEG signature with EFV.

Conclusions: A highly conserved EFV qEEG signature between rats, monkeys and humans makes this novel translational qEEG biomarker potentially useful for rapidly assessing the likelihood of CNS AEs in NNRTI drug development. The animal qEEG signal strength appeared to parallel the time course of reported clinical CNS AEs. Clinical studies of new NNRTIs may benefit from using qEEG to identify CNS adverse effect risk.

450 Neurocognition Following Antiretroviral Initiation in Behaviorally HIV-Infected Youth

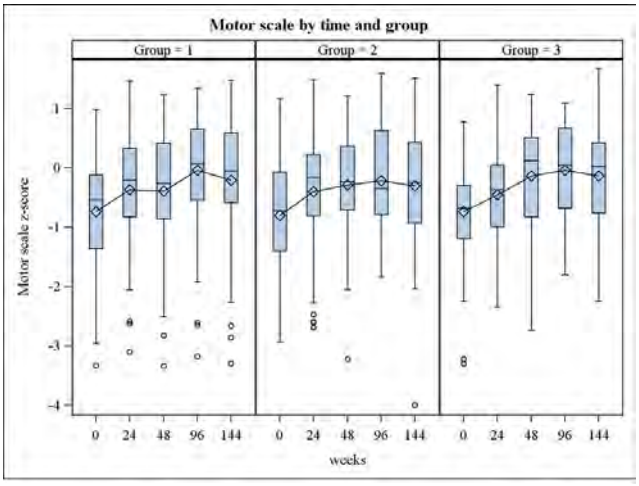
Sharon Nichols[1]; Patricia Garvie[2]; Tiandong Li[3]; Weijia Ren[3]; Bill Kapogiannis[4]; Bret Rudy[5]; John Sleasman[6]; Steven Woods[7]; Ana Puga[2]
The Adolescent Medicine Trials Network for HIV/AIDS Interventions

[1]University of California San Diego, La Jolla, CA, US; [2]Children's Diagnostic & Treament Center, Inc., Ft. Lauderdale, FL, US; [3]Westat, Inc., Rockville, MD, US; [4]National Institutes of Health (NIH), Bethesda, MD, US; [5]New York University, New York, NY, US; [6]Duke University, Durham, NC, US; [7]University of California, San Diego, La Jolla, CA, US

Background: Evidence suggests adolescents and young adults (youth) living with behaviorally acquired HIV (YLWH) are at risk for cognitive impairments. However, the role of HIV in these impairments and their potential to improve with antiretroviral therapy (ART) are unclear. The purpose of this study was to examine the impact of ART initiation and its timing on neurocognitive functioning in YLWH.

Methods: Data are from a prospective observational study supported by the Adolescent Medicine Trials Network for HIV/AIDS Interventions. Treatment naïve YLWH ages 18-24 at entry completed baseline and four additional assessments of attention/working memory, complex executive functioning, and motor functioning over three years. Group 1, co-enrolled in early ART initiation study, initiated ART at enrollment CD4>350 (n=56); Group 2 had CD4>350 and were not initiating ART (n=66); and Group 3 initiated ART with CD4<350 (n=59) per standard of care treatment guidelines at the time. Treatment was de-intensified to boosted Protease Inhibitor monotherapy at 48 weeks for those in Group 1 with suppressed viral load (n=35). Analyses used hierarchical linear modeling. Covariates included demographic, behavioral, and medical history variables.

Results: Participants were predominantly male (80.7%), non-Hispanic Black/African-American (65.2%) or Hispanic (22.7%), self-identified as gay or bisexual (71.2%), and high school educated or beyond (72.3%), with 40.8% currently in school. All groups showed improved performance over time with peak at 96 weeks in all three functional domains (e.g., see Figure for change in Motor scale by group over time). Trajectories of change were not significantly associated with treatment, timing of treatment initiation, or ART de-intensification. Demographic variables and comorbidities were associated with baseline functioning but did not directly interact with change over time. Baseline cognitive functioning predicted change in some domains but did not interact with treatment.



Motor scale by group over time

Conclusions: YLWH showed improvement in neurocognitive functioning over time that may be related to practice effects and nonspecific impact of increased services and support from study participation. Neither improvement nor decline in functioning was associated with timing of ART initiation or therapy de-intensification. In light of this, exploration of alternative pharmacological, cognitive, and behavioral interventions for management of neurocognitive dysfunction in YLWH may be warranted.

WEDNESDAY, FEBRUARY 25, 2015

Session P-G3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Neurologic Disorders in Resource-Limited Settings

451 Neurocognitive Impairment in Diverse Resource-Limited Settings: The International Neurological Study ACTG A5199 and A5271

Kevin R. Robertson[1]; Hongyu Jiang[2]; Scott Evans[2]; Christina Marra[4]; Baiba Berzins[3]; James Hakim[5]; Ned Sacktor[6]; Thomas Campbell[7]; Ann Walawander[8]; Jeff Schouten[4]
On behalf of ACTG 5199 and 5271

[1]University of North Carolina Chapel Hill, Chapel Hill, NC, US; [2]Harvard University, Boston, MA, US; [3]Northwestern University, Chicago, IL, US; [4]University of Washington, Seattle, WA, US; [5]University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe; [6]Johns Hopkins University, Baltimore, MD, US; [7]University of Colorado, Denver, CO, US; [8]Frontier Science, Amherst, NY, US; [9]University of Washington, Seattle, WA, US

Background: While neurocognitive impairment in HIV remains prevalent despite potent antiretroviral therapy (ART), there is a lack of infrastructure for conducting neurological research in resource limited settings (RLS), including normative data needed for clinical interpretation. A5271 provided training of clinical site personnel and collected normative comparison data. Here we provide estimates of neurocognitive impairment in seven RLS countries for HIV+ ART-naive participants from ACTG 5199.

Methods: We provided training for site personnel and collected normative comparison data on 2400 high risk HIV negatives from 10 VCT sites aligned with ACTG PEARLS (5175) in seven countries: Brazil (n=240), India (n=480), Malawi (n=481), Peru (n=239), South Africa (480), Thailand (n=240) and Zimbabwe (n=240) which was then utilized to create mild, moderate and severe impairment ratings. Associations were estimated from linear and logistic regression models using generalized estimating equations.

Results: Of the 860 HIV+ enrolled in A5199, 54% had no neurocognitive impairment at baseline (Table 1). Mild neurocognitive impairment was found in 25%, moderate in 17% and severe in 3%. With the initiation of ART, the odds of neurocognitive impairment reduced 12% (95% CI: 9%, 14%) for every 24 weeks (p<.0001). At week 24, 62% were normal and at week 168, 72% were normal. At week 168, moderate reduced to 6% and severe to 0.5%. Mild impairment dropped slightly, and then remained at about 18% out to week 168. Analyses indicated that drop out did not account for improvement. There were no differences between treatment arms. There were differences between countries in overall neurocognitive performance as expected (p<.0001).

Table 1: Summary of Impairment Ratings over Time

Impairment Rating	*Week*									
N										
Column %	*0*	*24*	*48*	*72*	*96*	*120*	*144*	*168*	*192*	*216*
Normal	466	513	479	462	394	359	335	310	220	43
	54.2	62.0	61.6	67.3	71.3	73.1	69.1	71.8	78.3	81.1
Mild	214	179	164	139	101	91	96	81	44	8
	24.9	21.6	21.1	20.2	18.3	18.5	19.8	18.8	15.7	15.1
Moderate	144	103	95	65	46	31	42	26	9	0
	16.7	12.6	12.2	9.5	8.3	6.3	8.7	6.0	3.2	0.0
Severe	29	13	9	6	2	2	2	2	2	1
	3.4	1.6	1.2	0.9	0.4	0.4	0.4	0.5	0.7	1.9
*Missing**	7	19	31	15	10	8	10	13	6	1
	0.8	2.3	4.0	2.2	1.8	1.6	2.1	3.0	2.1	1.9
Total with NP exams	860	827	778	687	553	491	485	432	281	53

* Missing means with missing values on NP exam forms

Conclusions: There was substantial prevalence of neurocognitive impairment at baseline in HIV+ ART naïve participants in diverse RLS. With ART, there were significant overall reductions in neurocognitive impairment over time, especially in those with moderate and severe impairments. The observed changes with ART may reflect both improvement and learning effect. ART in RLS led to reductions in neurocognitive impairment, and would likely lead to improved productivity and quality of life. A5271 provides infrastructure in diverse RLS, a much needed resource for clinicians and researchers conducting neurological and neuropsychological assessments.

452 High Frequency of Dementia in Antiretroviral-Naïve HIV+ Individuals in Rural Uganda

Ned Sacktor[1]; Deanna R. Saylor[1]; Gertrude Nakigozi[2]; Noeline Nakasujja[3]; Xiangrong Kong[4]; Kevin Robertson[5]; Ronald H. Gray[4]; Maria J. Wawer[4]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Rakai Health Sciences Program, Entebbe, Uganda; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]University of North Carolina, Chapel Hill, NC, US

Background: HIV dementia was seen in 31% of 81 antiretroviral (ARV) naïve HIV+ individuals in a previous study in Kampala, Uganda. The frequency and risk factors for each stage of HIV-associated neurocognitive disorder (HAND), *i.e.,* asymptomatic neurocognitive disorder (ANI), mild neurocognitive disorder (MND), and HIV dementia (HAD), in rural Sub-Saharan Africa is largely unknown. The objective of this study was to evaluate the frequency of and risk factors for HIV dementia in rural Rakai, Uganda where HIV subtypes D and A predominate.

Methods: 299 ARV naïve HIV+ and 210 HIV- individuals from the Rakai Community Cohort Study received detailed neurological history, examination, neuropsychological tests (including tests of verbal learning and memory, motor, psychomotor speed, executive function, and verbal fluency), functional assessments, CD4 count, and plasma viral load. HAND stage was determined using Frascati criteria combining clinical, neurological, functional, and neuropsychological test data. Results were compared to HIV- normative data obtained from the prior study in Kampala, Uganda.

Results: Demographics for HIV+ individuals were as follows: age [Mean (SD) = 36 (9) years, male gender % =51%, Education ≤ 4th grade % = 47%, CD4 count [Mean (SD) = 309 (159)]. There was no difference in age, gender, or education between HIV+ and HIV- individuals. HIV+ individuals were more likely to have dementia (27%) compared to HIV- individuals (7%), (p <0.001). There were no differences in less severe HAND categories between the HIV+ and HIV- groups. Risk factors for dementia included advanced age (p=< 0.001), subjective memory problems (p= 0.03), HIV seropositivity (p=<0.001), depression symptomatology (p= <0.001), and impaired performance on the International HIV Dementia Scale screening test (p=<0.001).

Conclusions: In one of the largest studies of cognitive performance and HAND in rural Sub-Saharan Africa, HIV+ individuals were more likely to have dementia compared to demographically matched HIV- individuals. Future studies will evaluate the frequency of HAND using HIV- normative data currently being obtained in Rakai, the association of HIV dementia and subtype, and response to ARV treatment.

453 Validation of the International HIV Dementia Scale Screening Tool for HAND in Uganda

Megan M. Hosein[1]; Deanna Saylor[1]; Gertrude Nakigozi[2]; Noeline Nakasujja[3]; Xiangrong Kong[4]; Kevin Robertson[5]; Ronald H. Gray[4]; Maria J. Wawer[4]; Ned Sacktor[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Rakai Health Sciences Program, Kalisizo, Uganda; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]University of North Carolina Chapel Hill, Chapel Hill, NC, US

Background: HIV-associated neurocognitive disorders (HAND) are prevalent and often under-diagnosed complications of HIV. The International HIV Dementia Scale (IHDS) has been validated as a useful screening tool for HIV-associated dementia (HAD) in a number of settings, including Kampala, Uganda. However, little is known about the utility of the IHDS in rural sub-Saharan Africa. The objective of this study was to assess the validity of the IHDS as an appropriate screening tool for detecting different levels of HAND in the rural district of Rakai, Uganda.

Methods: 299 HIV+ antiretroviral treatment (ART) naïve participants in the Rakai Community Cohort Study underwent comprehensive standardized neurological, neuropsychological and functional assessments, including the IHDS. HAND stages were determined based on the Frascati criteria. The diagnostic validity of the IHDS was assessed by determining the sensitivity, specificity, predictive values and area under the ROC curve (AUC) for IHDS cut-off scores of 9, 9.5 and 10 (lower score= worse performance).

Results: Participants' demographics were: Mean(SD) age = 36(9) years; Male = 51%; Education ≤ 4th grade = 47%; Mean(SD) CD4 count = 309(159). For detecting any level of HAND [asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HAD], an IHDS cut off of ≤9 had a sensitivity and specificity of 60% and 71% (AUC 0.66), while a cut-off of ≤9.5 had a sensitivity and specificity of 67% and 64% (AUC 0.66), and a cut-off of ≤10 had a sensitivity and specificity of 80% and 55% (AUC 0.68). For detecting symptomatic HAND (MND and HAD), a ≤9 cut-off had a sensitivity and specificity of 62% and 62% (AUC 0.62), ≤9.5 had a sensitivity and specificity of 70% and 54% (AUC 0.62), and ≤10 had a sensitivity and specificity of 83% and 44% (AUC 0.64). For detecting HAD, an IHDS ≤9 cut-off had a sensitivity and specificity of 75% and 54% (AUC 0.65), ≤9.5 had a sensitivity and specificity of 80% and 46% (AUC 0.63), and ≤10 had a sensitivity and specificity of 90% and 32% (AUC 0.61).

Conclusions: The IHDS is a sensitive and potentially useful screening tool for neurocognitive impairment in rural Uganda. When used for screening in a setting with comprehensive neuropsychological testing to confirm a HAND diagnosis, the ≤10 cut-off may be most useful as it provides the highest sensitivity. However, if further neuropsychological testing is unavailable, the higher specificity of a ≤9 cut-off may be more appropriate, particularly for HIV dementia screening.

454 Cerebrospinal Fluid Cytokines and HIV-Associated Neurocognitive Disorders in Uganda

Mahsa Abassi[1]; Gertrude Nakigozi[3]; Noeline Nakasujja[2]; Xiangrong Kong[4]; David B. Meya[2]; Kevin Robertson[5]; Ronald H. Gray[4]; Maria J. Wawer[5]; Ned Sacktor[5]; David R. Boulware[1]

[1]University of Minnesota, Minneapolis, MN, US; [2]Infectious Disease Institute, Kampala, Uganda; [3]Rakai Health Sciences Program, Entebbe, Uganda; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: In antiretroviral (ARV) naïve HIV+ individuals and HIV subtype B infection in the US, HIV associated neurocognitive disorder (HAND) is associated with increased cerebrospinal fluid (CSF) inflammatory cytokines. To better understand the neurocognitive effects of HIV in Uganda where HIV subtypes D and A predominate, we compared the expression of varying cytokines and neurodegenerative biomarkers in the CSF of ARV naïve HIV+ adults in Rakai, Uganda.

Methods: Participants (78) from the Rakai Community Cohort Study in Uganda, who were HIV+, age >20 years, and ARV naïve underwent CSF biomarker profiling via multiplex assay, assessing 17 cytokines and 20 neurodegenerative biomarkers. Neuropsychological testing was performed to determine HAND staging via the Frascati criteria as normal, asymptomatic neurological impairment (ANI), mild neurocognitive disorder (MND) and HIV dementia (dem). We compared CSF profiles by CD4 group and neurocognitive status, adjusting for multiple comparisons.

Results: Among 78 participants, 38 had CD4<200 with no active opportunistic infections, and 40 had moderate immunosuppression (CD4 351-500 cells/mcL). Neurocognitive function was found as normal (n=10), ANI (n=13), MND (n=33), and dementia (n=22). Persons with CD4<200 had significantly higher levels of several cytokines than those with CD4>350 (Table 1). Additionally, IL-2, IL-4, and MMP-1 were 100% detectable in CSF in persons with CD4<200 but detectable in 33%, 33%, 37%, respectively, among CD4>350 (P<0.001). IL5 was also more frequently detectable (76% vs. 33%, P=0.008). There was also lower levels of amyloid β42 (P<.001) in persons with CD4<200. When comparing persons with normal or ANI function vs. MND or dementia, those with MND or dementia had higher geometric mean levels of IFN-G (7.4 pg/mL vs. 2.5 pg/mL; P=0.036) after adjusting for CD4.

Table: Median Values of CSF Cytokines Measured in the CSF of HIV+ Adults in Uganda

Biomarker	CD4 <200 cells/μL (N=38)	CD4 350-500 cells/μL (N=40)	Univariate P-value	Adjusted P-value *
IL-2	3.7 (0.93, 1.06)	0.55 (1.02-1.3)	<0.001	<0.001
IL-4	0.47 (0.47-0.68)	<0.25 (<0.25-0.44)	0.001	0.008
IL-6	13 (9.7-19)	9.7 (5.9-17)	0.002	0.03
IL-7	2.3 (1.8-3.5)	1.4 (0.25-3.5)	0.003	0.034
IL-12	4.7 (3.9-5.6)	<0.25 (<0.25-2.3)	<0.001	<0.001
GM-CSF	176 (144-235)	40 (31-50)	<0.001	<0.001
MMP-1	6.0 (5.0-7.1)	<1.5 (<1.5 – 2.7)	<0.001	<0.001
MMP-7	116 (97-128)	49 (49-49)	<0.001	<0.001
MMP-10	11.0 (8.4-14.6)	7.0 (<2.5 -12.8)	0.020	0.244
Amyloid β42	843 (379-1781)	4262 (1740-7989)	<0.001	<0.001
sVCAM-1	21652 (14596-42992)	13574 (8579-26007)	0.008	0.101
S100B	1026 (785-1338)	589 (335-947)	0.005	0.068

Median values in pg/mL with interquartile range (IQR).
* Adjusted P values using the Holm's-Bonferoni method to adjust for multiple comparisons.

Conclusions: Persons with CD4<200 have higher levels of inflammatory cytokines (IL-6, MMP-1, MMP-7), T-cell growth factors (IL-2, IL-7), Th1 cytokine (IL-12), Th2 cytokines (IL-4, IL-5), and lower levels of amyloid β42 present in the CSF as compared to those with CD4 >350. Lower levels of amyloid β42 may be secondary to degradation by reactive astrocytes and microglial cells. Those with MND or dementia also have higher mean levels of INF-G than those classified as normal or ANI. The differences in CSF cytokine and neurodegenerative biomarker expression suggest that inflammation plays an important role in the progression of immunodeficiency in HIV+ adults.

455 A Comparison of 5 Brief Screening Tools for HAND in the USA and South Africa

John A. Joska[1]; Jade Witten[1]; Kevin Thomas[1]; Corne Robertson[1]; Martine Casson-Crook[1]; Heidi Roosa[2]; Jason Creighton[2]; Jennifer Lyons[3]; Justin McArthur[2]; **Ned Sacktor**[2]
[1]University of Cape Town, Cape Town, South Africa; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US

Background: A screening test for HIV associated neurocognitive disorders (HAND) is urgently needed in busy HIV clinics. We compared the sensitivity and specificity of five brief screening tools for HAND and HIV-dementia. We hypothesised that the International HIV Dementia Scale (IHDS), the Montreal Cognitive Assessment (MOCA) and the Cognitive Assessment Tool-rapid version (CAT-rapid) would be more sensitive than the Mini-Mental State Examination (MMSE) and the Simioni Symptom Questions (SSQ) in screening for HIV-D and all types of HAND.

Methods: We recruited individuals established on CART in Cape Town, South Africa, and Baltimore, USA. Participants underwent the 5 screening tests, a neuropsychological test battery, an assessment of activities of daily living, subjective adherence measures and neuromedical assessment, and cases were classified into HAND categories. We calculated the sensitivity and specificity of each tool to correctly identify HIV-D and any form of HAND (including ANI, MND and HIV-D) across the full sample, using a receiver operating characteristic analysis.

Results: The sample included 156 participants (89 from SA, 67 from the USA): median age of 40 years, 11 years of education, % women=62.80%, median CD4 cell count=460 cells/ml. Nearly half of the participants had symptomatic HAND [46 were classified as mild neurocognitive disorder (MND) and 19 as having dementia (HIV-D)]. To screen for HIV-D, using conventional cut-offs, the IHDS, MOCA, SSQ the CAT-Rapid displayed fair to good sensitivities of 68%, 100%, 79% and 94% respectively, while the MMSE was poor with a sensitivity of 26%. The specificities of the tools varied, with scores of 86% (IHDS), 23% (MOCA), 32%(SSQ) and 52% (CAT-rapid) respectively. To screen for HAND the sensitivities were as follows: IHDS (41%), MOCA (89%), SSQ (78(%), and CAT-rapid (52%), MMSE (24%). To screen for HAND the specificities were as follows: IHDS (86%), MOCA (22%), SSQ (32%), CAT-rapid (52%), and MMSE 98%).

Conclusions: The IHDS and CAT-rapid performed similarly and seem to be useful tools to screen for dementia and any form of HAND, while the MMSE showed poor sensitivity, and the MOCA and SSQ showed poor specificity.

456 Subtype Associations With HIV-Associated Neurocognitive Dysfunction

Tyler R. Day; Davey M. Smith; Robert Heaton; Donald Franklin; Myres W. Tilghman; Josué Pérez-Santiago
University of California San Diego, San Diego, CA, US

Background: Despite effective antiretroviral therapy, HIV-associated neurocognitive disorders (HAND) continue to be a problem. Many factors, including CD4 count and nadir, HIV viral load and HIV-1 subtype, have been associated with HAND. However, variability of the associations of these factors including subtype with HAND has not been evaluated in ethnically and culturally similar populations in Asia. We investigated several clinical and immunological markers in two different provinces of China, Anhui and Yunan, and evaluated the influence of HIV-1 subtype on association with HAND.

Methods: Blood-derived HIV-1 *env* sequences were obtained from 124 subjects in Anhui and 184 subjects in Yunan. We determined the infecting subtype (B, C or B/C) by evaluating for inter-subtype recombination using the Recombinant Identification Program 3.0 and TreeMaker on LANL. As a measure of viral diversity, we calculated a mixed base index (MBI) based on the number of ambiguous bases and the length of each sequence. We evaluated subtype, MBI, and clinical and demographical variables in the context of neurocognitive impairment (NCI), defined as having a global deficit score >0.5 based on a standardized neurocognitive battery. Statistical analyses were performed using R software.

Results: Including subjects from both regions, we found that individuals with NCI had significantly lower nadir (p=0.0005) and absolute (p=0.03) CD4 counts than those without NCI (Mann-Whitney test). Higher viral population diversity (MBI), lower CD4 nadir counts and lower CD4 absolute counts were associated with worse impairment (r=-0.16, p=0.005, r=-0.17, p=0.003, and r=0.14, p=0.01, respectively) by regression analysis. We also found that AIDS was significantly associated with HAND (p=0.001), but HIV-1 subtype was not associated with presence of HAND (p=0.35) by Fisher test. In a multivariate analysis that included HIV-1 subtype, results from all analyses remained similar except for CD4 nadir, which became a trend only for the region of Yunan (p=0.06).

Conclusions: Multiple factors have been associated with HAND during HIV-1 B and non-B subtype infections, and infecting subtypes have been implicated in bot the incidence and severity of HAND. This study of ethnically and culturally similar individuals demonstrated that factors that have long been associated with HAND (i.e. CD4 nadir, AIDS, viral diversity) are more likely to be associated with HAND than differences in infecting subtypes B, C or B/C.

457 Peripheral Neuropathy at First-Line Failure and on Second Line in Sub-Saharan Africa

Alejandro Arenas-Pinto[1]; Jennifer Thompson[1]; Godfrey Musoro[4]; Helen Mussana[5]; Abbas Lugemwa[3]; Andrew D. Kambugu[2]; Aggrey Mweemba[6]; Sarah Walker[1]; Paton Nicholas[1]
On behalf of the EARNEST Trial Team

[1]University College London, London, United Kingdom; [2]Makerere University, Kampala, Uganda; [3]Joint Clinical Research Centre, Mbarara, Uganda; [4]University of Zimbabwe, Harare, Zimbabwe; [5]Joint Clinical Research Centre, Kampala, Uganda; [6]University Teaching Hospital, Lusaka, Zambia

Background: Sensory peripheral neuropathy (PN) remains a common complication in HIV-positive patients despite effective anti-retroviral therapy (ART). Data on PN during second-line cART is scarce.

Methods: We assessed PN using the ACTG Brief Peripheral Neuropathy Screen tool in patients failing first-line ART and for 96 weeks following a switch to PI-based second-line ART in the EARNEST trial. Patients were randomised to a PI (standardised to lopinavir/ritonavir) plus either 2/3 NRTIs (80% TDF-based) or raltegravir, or as PI monotherapy (after 12 week induction with raltegravir). Factors associated with PN were investigated using logistic regression.

Results: Symptomatic PN (SPN) prevalence was 22% at switch to second-line (N=1251) and was independently associated ($p<0.05$) with older age (OR=1.04 per year), female gender (OR=1.64), history of TB (OR=1.86), smoking (OR=1.61), higher plasma creatinine (OR=1.09 per 0.1mg/dl increase), lower CD4 cell count (OR=0.83 per doubling) and not consuming alcohol (OR=0.54). Overall, SPN prevalence decreased to 17% by week 96 ($p=0.0002$) following similar trends in all treatment groups ($p=0.30$). Asymptomatic PN (APN) increased over the same period from 21% to 29% ($p<0.0001$) and prevalence of signs suggestive of PN regardless of symptoms remained stable (44% and 46% at entry and week 96 respectively). At week 48 and 96, after adjusting for time updated associations above and CD4 count and viral load at switch, SPN was not associated with current CD4 count ($p=0.10$) or VL ($p=0.97$) but was strongly associated with TB ($p<0.0001$). Including exposure to isoniazid had a comparable effect to that of TB. By week 96, new SPN incidence was 10%, and SPN had resolved in 58% reporting SPN at switch. Isoniazid-based TB treatment was prescribed during study period to 18% of patients who developed incident SPN, but only to 6% of those patients who never developed SPN ($P<0.001$).

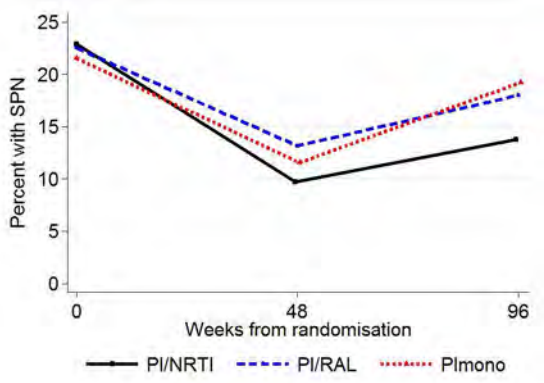


Figure: Percentage of Patients with SPN

Conclusions: SPN prevalence was significantly reduced with PI-based second-line therapy in all treatment groups, but we did not find any advantage to the NRTI-free regimens tested in EARNEST. The increase of APN and stability of PN-signs regardless of symptoms over 96 weeks suggest that there may be an underlying trend of neuropathy progression that may be masked by reduction of symptoms accompanying general health improvement induced by second-line ART. In addition to other known risk factors such as age, female gender and low CD4 count, SPN was strongly associated with exposure to isoniazid to treat TB.

458 Prevalence of and Risk Factors for Peripheral Neuropathy in Rakai, Uganda

Deanna R. Saylor[1]; Gertrude Nakigozi[2]; Noeline Nakasujja[3]; Xiangrong Kong[4]; Kevin Robertson[5]; Ronald H. Gray[4]; Maria J. Wawer[4]; Ned Sacktor[1]

[1]Johns Hopkins School of Medicine, Baltimore, MD, US; [2]Rakai Health Sciences Program, Entebbe, Uganda; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]University of North Carolina, Chapel Hill, NC, US

Background: Peripheral neuropathy (PN) is a common and potentially debilitating neurologic complication of HIV infection. Systematic studies to identify the prevalence of and risk factors for PN in sub-Saharan Africa are lacking.

Methods: A sample of participants in the Rakai Community Cohort Study underwent detailed neurological evaluation including assessment of demographic characteristics, subjective PN symptoms, and a neurological examination by a trained medical officer. PN was defined as $\geq$ 1 sign on examination (e.g. decreased pinprick or vibration in the fingers or toes, distal weakness, or reduced/ absent ankle reflexes) and $\geq$ 1 subjective symptom (e.g. paresthesias, numbness, or pain in the hands or feet). PN risk factors were determined by comparing characteristics of participants with and without neuropathy using t-tests for continuous variables and chi-squared tests for categorical variables.

Results: 538 participants were enrolled: 200 HIV-positive (HIV+) antiretroviral (ARV) naïve participants with moderate immunosuppression (CD4 count 351-500), 107 HIV+ ARV-naïve participants with advanced immunosuppression (CD4 count <200), and 231 age and gender-matched HIV-negative (HIV-) participants. There were no demographic differences between HIV+ and HIV- participants, but HIV+ participants with advanced immunosuppression were younger (34 years vs. 37 years, $p=0.002$), more likely to be male (62% vs. 45%, $p=0.004$), and had lower body mass indexes (BMI) (20.7 vs. 23.0, $p<0.001$) than those with moderate immunosuppression. PN was more prevalent among HIV+ than HIV- participants (24% vs. 8%, $p<0.001$) and showed a trend toward statistical significance among HIV+ participants with advanced immunosuppression versus those with moderate immunosuppression (30% vs. 20%, $p=0.05$). In addition to HIV status and level of immunosuppression, older age (mean: 38 years vs. 35 years, $p=0.03$) was also a significant predictor of PN, but BMI ($p=0.45$), alcohol use ($p=0.78$), and prior isoniazid use ($p=0.06$) were not. PN severity was worse in HIV+ than HIV- participants as assessed by the Modified Total Neuropathy Scale ($p=0.003$).

Conclusions: PN is prevalent in rural Uganda and is more common in HIV+ individuals, with a trend toward increased prevalence in those with advanced disease. PN prevalence also increases with age. This highlights the need for early diagnosis and treatment of HIV to prevent this potentially debilitating complication and the necessity of close monitoring for PN as the HIV+ population ages.

459 Predictors of Cognitive Performance Among HIV-Infected Patients in East Africa

Victor G. Valcour[1]; Francis Kiweewa[2]; Rosemary Namagembe[2]; Rither Langat[3]; Samoel Khamadi[4]; Kyra Hansson[1]; Christina S. Polyak[5]; Julie Ake[5]
On behalf of the RV329 AFRICOS Study Team

[1]University of California San Francisco, San Francisco, CA, US; [2]Walter Reed Project, Kampala, Uganda; [3]Walter Reed Project, Kericho, Kenya; [4]Walter Reed Project - Tanzania, Mbeya, United Republic of Tanzania; [5]Walter Reed Army Institute of Research, Silver Spring, MD, US

Background: Cognitive impairment remains a frequent complication of HIV despite access to antiretroviral therapy. Few data exist regarding risk factors in resource-limited settings.

Methods: The African Cohort Study (AFRICOS) aims to longitudinally assess the impact of clinical practices, biological factors and socio-behavioral issues on HIV infection and disease progression in an African context. All enrollees undergo the International HIV Dementia scale (IHDS), an auditory verbal learning and delayed recall task (AVLT-DR), the grooved pegboard (GP) test in both hands, the Trail Making A test and an action fluency task. We examined factors that correlate to neuropsychological testing performance including CD4 count, nadir CD4 count, plasma HIV RNA, age, educational attainment, infectious and non-infectious comorbidities among other clinical variables from data captured in Kenya, Uganda, and Tanzania.

Results: 779 HIV-infected and 149 HIV-uninfected subjects were evaluated. The HIV-infected group was 58% female, had a mean (SD) age of 41 (10) and 63% had 6 or fewer years of education. 73% were taking combination antiretroviral therapy at the time of testing. Mean (SD, range) IHDS was 8.7 (1.7, 1-12) for the HIV infected group compared to 9.0 (1.7, 3-12) for the HIV-uninfected controls ($p = 0.022$). HIV status, age, and educational attainment were all associated with performance on all tests ($p's<0.02$). CD4 nadir count was associated with AVLT-DR ($p=0.003$) and at trend level for GP dominant hand ($p=0.096$). We found no association between cognitive performance and the number of infectious nor non-infectious comorbidities.

Conclusions: This study investigated correlates to neuropsychological performance in over 900 study participants from East Africa. Cognitive impairment is associated with HIV-infection, age and educational attainment. Similar to findings from resource-rich regions, CD4 nadir count was associated with performance on two tests. Unlike resource-rich areas, where cognition is increasingly associated with non-HIV factors, the number of comorbidities did not correlate to cognitive performance, a factor that may be due to the relative younger age of the group.

THURSDAY, FEBRUARY 26, 2015

Session P-G4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HAND Genetics

460 Mitochondrial DNA Haplogroups and CSF Neuroinflammation in the CHARTER Cohort

Todd Hulgan[4]; David Samuels[4]; Ronald J. Ellis[1]; William Bush[2]; Scott Letendre[1]; Donald Franklin[1]; Igor Grant[1]; Asha R. Kallianpur[3]
CHARTER Group

[1]University of California San Diego, San Diego, CA, US; [2]Case Western Reserve University, Cleveland, OH, US; [3]Cleveland Clinic Foundation, Lerner Research Institute, Cleveland, OH, US; [4]Vanderbilt University, Nashville, TN, US

Background: Neurocognitive impairment (NCI) remains an important complication in the combination antiretroviral therapy (CART) era, and is associated with neuroinflammation in cerebrospinal fluid (CSF). Mitochondrial DNA (mtDNA) haplogroups are ancestry-related patterns of single-nucleotide polymorphisms that are associated with differential mitochondrial function in model systems, neurodegenerative diseases in HIV-uninfected populations, and HIV- and CART-associated outcomes in HIV-infected persons. We hypothesized that mtDNA haplogroups would be associated with neuroinflammation in HIV-infected adults.

Methods: CHARTER is a U.S.-based observational study of HIV-infected adults who underwent standardized neurocognitive assessments. Participants without confounding neurocognitive comorbidities and who consented to DNA collection underwent mtDNA sequencing from whole blood. A subset also underwent lumbar puncture. IL-6, IL-8, TNF-α (high-sensitivity), VEGF, IP-10, and novel soluble biomarkers of brain iron homeostasis, antioxidant defense, and inflammation- ceruloplasmin (CP) and haploglobin (HP)- were measured in CSF by immunoassay. Haplogroups were assigned using HaploGrep. Multivariable regression of mtDNA haplogroups and log-transformed CSF biomarkers were stratified by genetic ancestry using whole-genome nuclear DNA genotyping (European [EA], African [AA], or admixed Hispanic ancestry [HA]), and adjusted for age, sex, CART, detectable CSF HIV RNA, and CD4 nadir.

Results: Haplogroups could be assigned in 385 subjects with evaluable CSF (45% EA, 44% AA, 11% HA, 20% female, median age 43 years, CD4 nadir 175 cells/mm^3, 74% on CART). Statistically significant adjusted haplogroup-biomarker associations included higher IP-10 in HA subjects with haplogroup B ($N=12$; $p=0.03$) and higher CP with haplogroups L1 ($N=32$) and L2 ($N=52$) in AA subjects ($p=0.02$ and 0.01, respectively). Among EA subjects, mtDNA haplogroups were not significantly associated with these CSF biomarkers. Several additional associations of IL-6, IL-8, IP-10, and TNF-α with age, sex, CD4 nadir, CSF HIV detectability, and CART were observed independent of mtDNA haplogroup.

Conclusions: We observed associations between mtDNA haplogroups and CSF IP-10 and CP in HA and AA CHARTER subjects, respectively, independent of other potential confounders. These preliminary results suggest novel mechanisms of neuroinflammation and perhaps NCI that merit further exploration.

461 Iron-Regulatory Genes Are Associated With Neuroimaging Traits in HIV Infection

Tricia A. Thornton-Wells[2]; Christine Fennema-Notestine[3]; Todd Hulgan[4]; Scott Letendre[5]; Ronald J. Ellis[6]; **Asha R. Kallianpur**[1]; for the CHARTER Group[7]

[1]Cleveland Clinic/Lerner Research Institute, Cleveland, OH, US; [2]Vanderbilt University School of Medicine, Nashville, TN, US; [3]University of California San Diego, San Diego, CA, US; [4]Vanderbilt University School of Medicine, Nashville, TN, US; [5]University of California San Diego, San Diego, CA, US; [6]University of California San Diego, San Diego, CA, US; [7]University of California San Diego (UCSD), San Diego, CA, US

Background: HIV-Associated Neurocognitive Disorders (HAND) remain highly prevalent, despite viral suppression with combination antiretroviral therapy. Structural and metabolic changes in the brain may occur early in HIV-infection and represent important endophenotypes of HAND. Since brain iron dysregulation is a common feature of neurodegenerative disorders and iron is linked to immune regulation, we hypothesized that iron-regulatory-gene variants contribute to neuroimaging traits in HIV-infected persons with or without HAND.

Methods: We genotyped 250 SNPs in 12 iron-related genes and evaluated their associations with magnetic resonance (MR) imaging traits in 243 subjects with neuroimaging data from CHARTER, a multicenter, observational neuro-HIV study. Structural MR imaging measurements of gray matter (GM) and white matter (WM) volume and MR spectroscopy measurements of brain metabolites were made in 21 regions of interest (ROI); T2* images were unavailable. Multivariable regression models of log-transformed neuroimaging

variables were adjusted for age, scanner, genetic ancestry, CD4+ T-cell nadir, HIV RNA detectability in plasma, and trait-specific covariates. Analyses stratified by the presence of neurocognitive impairment (Global Deficit Score <0.5 or ≥0.5), virus detectability, or comorbidities were also performed, and two levels of correction for multiple statistical tests were applied.

Results: Of 22 common SNPs that were significantly associated with structural and/or metabolic traits after correction for the 37 haplotype blocks represented ($p<0.05$), 5 SNP associations also survived the most conservative correction (for 37 haplotype blocks and 21 ROI) and demonstrated biologically plausible patterns of association with traits previously linked to aging and/or HAND (Table). Iron-regulatory genes with significant associations included: *TFRC* in subjects with detectable HIV RNA, *SLC40A1* in subjects with undetectable viral RNA, *SLC11A1* in subjects without neurocognitive impairment, and *CP* and *ACO2* in subjects with comorbidities.

SNP (Allele)	Gene	Neuroimaging Trait	Adjusted Odds Ratio	*p*-value
rs13404407 *(C)*	SLC40A1	Abnormal WM volume	2.466	2.23E-06
rs17091382 *(A)*	TFRC	Subcortical GM volume	0.907	3.23E-05
rs4974389 *(A)*	CP	Basal ganglia choline	1.049	3.52E-05
rs7576974 *(T)*	SLC11A1	Frontal GM N-acetylaspartate	1.041	3.62E-05
rs9611598 *(A)*	ACO2	Subcortical GM volume	0.729	5.94E-05

Conclusions: Iron-regulatory gene variation is associated with degenerative neuroimaging traits in HIV-infected persons, such as abnormal WM and subcortical GM volumes, and with regional metabolite levels that reflect brain inflammation and neuronal integrity. Further studies are needed to replicate these findings, incorporate iron-sensitive neuroimaging (*e.g.*, T2*), and assess contributions of these variants to neurodegenerative sequelae of HIV infection, including HAND.

462 Synergistic Effects of *MBL2*/*APP* Polymorphisms on Neurocognitive Impairment in CHARTER

Kumud Singh; Qianqian Deng; Christine Fennema-Notestine; Florin Vaida; Ronald Ellis; Scott Letendre; Donald Franklin; Debralee Rosario; Robert Heaton; Igor Grant
CHARTER

University of California San Diego, La Jolla, CA, US

Background: Mannose binding lectin (MBL), coded by *MBL2*, recognizes mannose laden glycans on HIV-1 gp120 and activates complement for virus opsonization. Also, via its cysteine rich region, MBL interacts with amyloid beta (coded by *APP*) presumably for clearing it by complement mediated lyses. We hypothesized that the synergistic effects of polymorphisms in APP promoter (rs364048) that enhances APP expression and *MBL2* variants with lower MBL (*A/O*: rs1800450; rs1800451; rs5030737; *H/L*: rs11003125; *Y/X*: rs7096206; and *P/Q*: rs7095891), will predict neurocognitive (NC) outcomes in HIV-infected adults.

Methods: Of 563 subjects from the CHARTER (CNS HIV AntiRetroviral Therapy Effects Research) longitudinal cohort, 399 were on highly active antiretroviral therapy (HAART), 79 on non-HAART and 85 were antiretroviral-naive. 244 subjects were evaluated with single voxel magnetic resonance spectroscopy for brain metabolites choline (CHO), creatine (CR), N-Acetylaspartate (NAA) and myo-inositol (MI) in frontal white matter (FWM), frontal gray matter (FGM) and basal ganglia using LC Model. Associations of genotypes with neuroimaging outcomes were cross-sectionally examined by multivariate linear regression. Analyses adjusted for comorbidity, current CD4>=200, nadir CD4>=200, detectable plasma/CSF HIV RNA, and HCV serostatus. NC endpoints included global deficit score (0-5), global neurocognitive impairment (NCI, yes/no), and HIV-associated neurocognitive disorders (HAND). Logistic regression for comparing genotypes and Bonferroni correction were used.

Results: Of 563 subjects, 79% were males; 54% White and 43% Black. Presence of *APP* rs364048 and *MBL2-A/O* variants was associated with abnormal FWM (p=0.014) and a strong trend for HAND in subjects on HAART (p=0.06). Presence of *MBL2-P/Q* and rs364048 in those with HAART predicted worse NCI (p=0.013) and HAND (Unimpaired MBL2-Y/X and rs364048, and on HAART were associated with NCI (p=0.047), HAND (p=0.033), and strong trends for higher FWM-NAA (p=0.047) and FWM-CR (p=0.06). Presence of *MBL2-H/L* and rs364048 in those on HAART also predicted higher FGM-NAA (p=0.012).

Conclusions: Synergistic effects of higher APP and lower MBL expression due to presence of *MBL2/APP* polymorphisms, potentially facilitate complement activation, neuroinflammation and brain abnormalities leading to neurocognitive impairment. *MBL2/APP* genotypes are potential predictive biomarkers for HAND.

463 No Association Between Apoε4, HIV Infection, Age, Cognitive Outcome or Death

James T. Becker[1]; Jeremy J. Martinson[1]; Sudhir Penugonda[2]; Lawrence Kingsley[1]; Samantha A. Molsberry[1]; Sandra Reynolds[3]; Andrew Levine[4]; Eileen Martin[5]; Cynthia A. Munro[6]; Ned Sacktor[6]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [4]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US; [5]Rush University Medical Center, Chicago, IL, US; [6]Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: The ε4 allele of the ApoE gene may have important interactions with physical health and cognitive function among individuals with HIV disease. The purpose of this study is to examine the relationships between ε4, HIV disease, age, incident neuropsychological impairment and death in a large, well-characterized study sample.

Methods: Among the men participating in the Multicenter AIDS Cohort Study (MACS) 2,846 had ApoE genotyping and neuropsychological test data available for analysis. Classifications of cognitive impairment were operationalized using the criteria outlined by Woods et al. (2004) and Antinori et al. (2007). We examined the unadjusted associations between ApoE and other variables using t-tests and contingency tables. Time to death or incident cognitive impairment was tested using Cox proportional hazard models.

Results: There was a significant association between race and ApoE genotype; 23.2% of the men who identified themselves as White had at least one copy of the ε4 allele, whereas 31.2% of the men in other races (primarily African-American) had at least one ε4 allele. We found a significant association between time to death and HIV infection status, as well as older age, race, and education; ApoE status was not significantly associated with time to death. We found a significant association between HIV infection and time to incident cognitive impairment, as well as age, and education; Apoε4 status was not related to incident cognitive impairment. There were no significant two-way interactions between ApoE, HIV, and age on cognitive impairment.

Conclusions: Our analysis found no association between ApoE genotype and the development of cognitive dysfunction or time to death. This does not preclude the possibility that ApoE may have an impact on specific cognitive functions or cognitive domains; however, our findings indicate that the transition from normal to impaired cognition is unaffected by ApoE ε4. These data replicate and strengthen prior findings of the lack of association between ApoE genotype and cognitive outcomes in HIV disease. We conclude that within the specific constraints of an exclusively male sample in which the majority of participants were younger than 65 years of age, the ApoE ε4 allele does not interact with HIV serostatus.

464 Bridging Genetics, Histopathology, and Neurocognition in the Context of HAND

Andrew Levine[1]; Virawudh Soontornniyomkij[2]; Cristian L. Achim[2]; Ben Gouaux[2]; Eliezer Masliah[2]; Janet Sinsheimer[3]; Elyse Singer[1]; David J. Moore[2]

[1]University of California Los Angeles, Long Beach, CA, US; [2]University of California San Diego, San Diego, CA, US; [3]University of California Los Angeles, Los Angeles, CA, US

Background: It is unclear which histopathological features of HIV underlie the symptoms of HIV-associated neurocognitive disorders (HAND). Host-genetic association studies have implicated a variety of risk alleles for HAND, but findings have been difficult to replicate due largely to the fact that the neuropsychological impairments common in HAND are heterogeneous across patients. Instead, focusing on intermediate phenotypes, such as histopathology, may serve two purposes: 1) to clarify which, if any, genetic variants contribute to HAND, and 2) to determine which histopathological markers are most relevant to HAND. This study attempts to bridge the gap between genetics, neuropathology, and behavior in the context of HAND.

Methods: We examined 82 HIV+ cases diagnosed within 1 year of death as neuropsychologically normal or as having HAND. Cases whose neuropsychological impairment was better attributed to other factors (e.g., stroke, TBI) were not included. The following histopathological markers were quantified from the frontal cortex, frontal white matter, putamen, and hippocampus: glial fibrillary acid protein (GFAP), ionized calcium binding adapter molecule-1, and amyloid-β (Aβ). Synaptophysin (SYP) and microtubule-associated protein-2 (MAP2) were also quantified in frontal cortex of 37 cases. DNA was extracted from occipital lobe and 24 immunological and neurobiological-related genes were genotyped. HIV disease characteristics and neuropsychological data were collected. Non-parametric tests were used due to the non-normal distribution of histopathological data, with Bonferroni correction for multiple comparisons.

Results: Global neurocognitive functioning was correlated with MAP2 (r= -.691, p<0001) and SYP (r= -.580, p<.0001) in frontal cortex. Of the virologic variables examined, only estimated years with HIV infection was correlated with GFAP in putamen (r = .421, p<.0001). GFAP in putamen and frontal grey matter was influenced by IL1- α genotype (p=.001).

Conclusions: Findings suggest that astrogliosis (GFAP) in subcortical brain structures increases with duration of infection (but not age), and that this is influenced by a pro-inflammatory IL1-α genotype. However, GFAP was not correlated with neurocognitive functioning or HAND. Instead, MAP2 and SYP in frontal cortex and Aβ in putamen were associated with HAND and neurocognitive functioning, indicating that neuronal integrity and communication are more directly associated with behavioral features of HAND.

TUESDAY, FEBRUARY 24, 2015

Session P-G5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HAND Diagnosis and Predictors

465 Relative Risk and Factors Associated With Progression to Symptomatic HAND

Sean B. Rourke[1]; John Gill[2]; Anita Rachlis[1]; Colin Kovacs[3]; Gordon Arbess[3]; Jason Brunetta[3]; Adriana Carvalhal[3]; Chris Power[2]; Ann N. Burchell[4]; Tsegaye Bekele[4]

[1]University of Toronto, Toronto, Canada; [2]University of Alberta, Calgary, Canada; [3]Maple Leaf Medical Clinic, Toronto, Canada; [4]The Ontario HIV Treatment Network, Toronto, Canada; [5]St. Michael's Hospital, Toronto, Canada

Background: HIV-associated neurocognitive disorders (HAND) remain prevalent and recent work by Grant and colleagues (2014) demonstrated that asymptomatic neurocognitive impairment (ANI) is associated with a 2-5 risk for the development of symptomatic HAND (mild neurocognitive impairment [MND] or HIV-associated dementia [HAD]) in persons followed in CHARTER. We were interested in replicating and extending these results in a Canadian sample.

Methods: Study sample included 575 adults who are enrolled in the Ontario HIV Treatment Network Cohort Study (OCS) and who were either neuropsychologically normal (NP-Normal; n=299) or had ANI (n=276) at baseline. Neuropsychological testing was done every 12 months (median follow-up time: 30 months) using a brief test battery that included Hopkins Verbal Learning Test- Revised (HVLT-R), Grooved Pegboard, and WAIS-R Digit Symbol. Cognitive complaints were assessed with four-item Medical Outcomes Study Cognitive Functioning scale. HAND status was assigned according Antinori et al., (2007) criteria. We used proportional hazards regression modelling to generate risk ratios for progression to MND or HAD after adjusting for baseline and time-varying covariates.

Results: Participants: 82% men, 64% Caucasian, 86% on cART, and 73% had undetectable HIV viral load at baseline. Over the follow-up period, 99 individuals (39 who were NP-N and 60 who had ANI at baseline) showed progression to MND or HAD. Participants with ANI had shorter time of progression to MND or HAD than those who were NP-Normal at baseline after adjusting for baseline and time-varying predictors: adjusted hazards ratio 1.85 (95% confidence interval: 1.12-2.82; p=0.005). Among the covariates examined, depression and current smoking were significant predictors of higher risk of progression, while undetectable plasma HIV viral load was significantly associated with lower risk of progression to MND or HAD . Low nadir CD4 (<200 cells/mm^3) was not a significant predictor of progression in adjusted analyses although it was associated with higher risk prior to adjustment for covariates.

Conclusions: Asymptomatic Neurocognitive Impairment is associated with almost two-fold increased risk of progression to symptomatic HAND. Early treatment with cART and addressing medical and mental comorbidities may delay or lower risk of the development and progression of symptomatic HAND.

466 Monocytes Activation Characterizes Immune Failure but Not Cognitive Impairment on ART

Antonio Muscatello[1]; Davide Mangioni[1]; Paolo Perseghin[2]; Arianna Incontri[2]; Alessandro Soria[1]; Nicola Squillace[1]; Giuseppe Lapadula[1]; Sebastiano Leone[1]; Andrea Gori[1]; **Alessandra Bandera**[1]

[1]S. Gerardo Hospital, Monza, Italy; [2]San Gerardo Hospital–UOS Aferesi e Nuove Tecnologie Trasfusionali–SIMT, Monza, Italy

Background: Neurocognitive impairment (NCI) in HIV+ patients can occur despite effective ART and has been linked to increased CD16-bearing monocytes in circulation. We evaluated monocytes (M/M) phenotypes and activation markers in HIV+ patients under ART, aiming to define the role of innate immune activation on CD4+ T cell recovery and NCI.

Methods: Cross sectional study: 84 HIV+ patients whit actual CD4+ T cell count ≤350/μl (n=39, Immune failure-IF) or ≥500/μl (n=45,Immune success-IS) after ≥18 months of ART and with VL<50 copies/ml for at least 12 months. The two groups were matched both by age and CD4+ T cell nadir. All patients participated in blood studies and a battery of 8 neuropsychological tests (NPZ8). Peripheral M/M phenotypes (distinguished based on CD14 and CD16 surface expression on "classical" CD14++CD16-, "intermediate" CD14++CD16+ and "non classical" CD14+CD16++) as well as surface activation markers (CD163, CD11b, HLA-DR, CD38, CD69) were evaluated by flow cytometry. Statistical analyses were performed using Wilcoxon and Chi-square.

Results: Compared to IS subjects, IF patients showed significantly lower levels of "classical"(p=0.05) and higher levels of "intermediate" monocytes (p=0.04). "Non classical" monocytes were not significantly different between groups. IF patients displayed significantly lower expression of CD163 compared to IS patients, both on total (p=0.02)

and "classical" monocytes (p=0.01). Regarding the expression of CD11b, IF patients showed significantly lower levels on "classical" monocytes (p=0.05) and higher levels on "intermediate" monocytes (p=0.05) compared to IS group. No differences in the expression of HLA-DR, CD38 and CD69 on M/M were found in the two groups. NCI was observed in 20/84 patients (19 defined as ANI and 1 as MND). NCI prevalence was not different between the two groups (25.7% in IF and 22.2% in IS). There was no correlation between overall NCI and monocyte phenotypes neither expression of activation markers on M/M.

Conclusions: A shift on M/M phenotype from the "classical" towards "intermediate" and altered expression of monocyte activation markers, CD163 and CD11b, correlate with immune failure on ART. HIV-infected subjects with NCI on ART do not have a distinct monocyte phenotype using the variable we studied.

467 The VACS Index Predicts Change in Neurocognitive Functions in People With HIV

Sean B. Rourke[1]; John Gill[2]; Anita Rachlis[1]; Amy Justice[7]; Colin Kovacs[3]; Gordon Arbess[4]; Jason Brunetta[3]; Adriana Carvalhal[4]; Chris Power[6]; Ann N. Burchell[5]

[1]University of Toronto, Toronto, Canada; [2]University of Alberta, Calgary, Canada; [3]Maple Leaf Medical Clinic, Toronto, Canada; [4]St. Michael's Hospital, Toronto, Canada; [5]The Ontario HIV Treatment Network, Toronto, Canada; [6]University of Alberta, Edmonton, Canada; [7]Yale University School of Medicine, New Haven, CT, US

Background: Recent work by Marquine et al (2014) has shown an association between higher Veterans Aging Cohort Study (VACS) Index and increased risk of neuropsychological (NP) impairment; but there is limited evidence on longitudinal association between the VACS index and NP functioning and the potential clinical utility of the VACS index for HAND.

Methods: Study participants were from recruited from the city of Toronto, Canada. Baseline and one follow-up NP assessments were done (median follow-up time: 12 months) using a brief NP battery that included Hopkins Verbal Learning Test- Revised (HVLT-R), Grooved Pegboard, and WAIS-R Digit Symbol tests. Overall NP functioning was assessed using an unadjusted raw NP score (z-score), demographically adjusted NP score (Global T-score), and summary regression-based change scores. The VACS Index was computed by summing pre-assigned risk points for age, CD4 count, plasma HIV viral load, haemoglobin, fibrosis, renal glomerular filtration, and HCV infection following guidelines. Hierarchical linear regression method was used to determine the association between the VACS index score at baseline and change in NP functioning adjusting for NP performance, demographic factors, cognitive symptoms, depression, HIV disease markers, and medical comorbidities at baseline.

Results: Data from 523 participants (78% male, 85% on ART, and 71% with suppressed viral load) were included in the analyses. In an unadjusted analyses, higher VACS index score at baseline was associated with a decline in overall NP function measured by changes in z-score (B= -0.06, p<0.001), summary regression-based score (B= -0.03, p=0.009), or Global T-score (B=-0.27, p=0.001). This association persisted after adjustment for baseline NP performance, cognitive symptoms, depression, HIV disease markers, medical comorbidities, and demographic variables. In adjusted analyses, higher VACS index score at baseline predicted a decline in raw NP z-score (B= -0.06, p<0.001), summary regression-based change score (B= -0.02, p=0.004), and Global T-score (B=-0.25, p<0.001). The VACS index score also accounted for considerable proportion (9% -17%) of the total variances explained by the regression models.

Conclusions: Our results validate recent findings from the CHARTER study and suggest that the VACS index may be a useful clinical tool to identify and target those at higher risk for HIV–associated Neurocognitive Disorders.

468 When Diagnosing HAND, Should Visuospatial Functioning be Evaluated?

Talia Shirazi[1]; Angela Summers[1]; Sally Steinbach[2]; Suad Kapetanovick[1]; Avindra Nath[2]; Bryan Smith[2]; Joseph Snow[1]

[1]National Institute of Mental Health (NIMH), Bethesda, MD, US; [2]National Institute of Neurological Disorders and Stroke, Bethesda, MD, US

Background: Prior research has demonstrated that visuospatial functioning is often deleteriously affected in HIV-Associated Neurocognitive Disorders (HAND). Nevertheless, tests of visuospatial abilities are often omitted in current HAND research. We sought to determine whether the addition of visuospatial measures to an established HIV neuropsychological battery would increase the rate of HAND diagnoses. Additionally, to determine the relative likelihood that visuospatial functioning is impaired in HAND, we compared the rate of deficit on a visuospatial test to that of other tests in an established battery.

Methods: Seventy HIV-seropositive (69 currently on ART) and 11 healthy control participants completed neuropsychological testing as part of a NIH Intramural HIV screening protocol (NCT01875588). Participants were administered the Benton Judgment of Line Orientation (JLO), a test of visuospatial abilities, as well as the CHARTER battery, an established HAND battery assessing attention, executive function, information processing, motor speed, verbal fluency, and memory.

Results: Using the CHARTER battery alone, 21.4% (15/70) of patients met criteria for HAND. However, with the addition of a visuospatial measure, HAND prevalence rose to 30% (21/70), an 8.6% increase. The rate of deficient performance on JLO in HIV patients was one of the highest observed (25.7%), fourth to PASAT, a measure of attention (28.6%), BVMT (a visual memory test) total recall (28.6%) and BVMT delayed recall (30%), with the average rate of individuals with deficient performance across all tests being 16% (see Table). Mean T-scores were significantly lower in patients than controls for the PASAT (t=2.1, *p*=0.04), BVMT total recall (t=2.25, *p*=0.03), BVMT delayed recall (t= 2.19, *p*=0.03), and JLO (t=3.26, *p*=0.004), but not on the other 11 of 14 CHARTER measures.

Table. Percentage of HIV+ and control participants with deficient scores as well as comparison of scores between HIV and control participants per neuropsychological measure

Measure	Domain	Percentage of controls	Percentage of HIV+ patients	HIV worse than control participants?
Paced Auditory Serial Addition Test	Attention	9.1	28.6	Yes (t=2.1, p=0.039)
WAIS-III Letter-Number Sequencing	Attention	0.0	5.7	No
Trail-Making Test B	Executive	0.0	12.9	No
WCST perseverative responses	Executive	27.3	22.9	No
Trail-Making Test A	Info Processing	0.0	10.0	No
WAIS-III Digit-Symbol Coding	Info Processing	18.2	14.3	No
WAIS-III Symbol Search	Info Processing	0.0	10.0	No
Letter (FAS) Fluency	Verbal	18.2	11.4	No
Category (animal) Fluency	Verbal	18.2	10.0	No
HVLT-R Total Recall	Learning	9.1	10.0	No
BVMT-R Total Recall	Learning	18.2	28.6	Yes (t=2.25, p=0.027)
Grooved Pegboard (most impaired hand)	Motor Speed	36.4	20.0	No
HVLT-R Delayed Recall	Memory	9.1	12.9	No
BVMT-R Delayed Recall	Memory	9.1	30.0	Yes (t=2.19, p=0.031)
Judgment of Line Orientation	Visuospatial	0.0	25.7	Yes (t=3.26, p=0.004)

Conclusions: Our preliminary data suggest that visuospatial functioning may be a commonly affected cognitive domain in HIV patients in the HAART era. The omission of visuospatial measures on established HAND batteries may lead to an incomplete understanding of the neuropsychological impairments associated with HIV, as well as to possibly underestimating HAND prevalence. Future research should consider evaluating visuospatial functioning in addition to the other commonly assessed cognitive domains.

469 Predictors of Neurocognitive Decline Among Aviremic Individuals in the CHARTER Cohort

Marie-Josée Brouillette[1]; Tracy Yuen[2]; Susan C. Scott[2]; Lesley K. Fellows[3]; Robert Heaton[4]; Scott Letendre[4]; Ronald J. Ellis[4]; Nancy Mayo[2]
the CHARTER group

[1]McGill University Health Centre, Montreal, Canada; [2]McGill University Health Centre, Montreal, Canada; [3]Montreal Neurological Hospital, Montreal, Canada; [4]University of California San Diego, San Diego, CA, US

Background: Limited information is available on the predictors of neurocognitive (NC) *decline* in individuals with good virological control. Identification of modifiable risk factors that predict decline would support the development of targeted interventions aimed at minimizing NC decline in higher-risk individuals. The objective of the study was to identify baseline factors predicting NC decline over the subsequent 3 years in aviremic individuals.

Methods: As part of the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study, HIV+ individuals were administered 15 neuropsychological tests every 6 months. Group-based trajectory analysis was used to detect patterns of NC change on each test over the course of follow-up. Individuals who deteriorated ≥ 0.5 SD on at least 1 test within the first 36 months of follow-up were considered decliners. Multiple logistic regression was used to identify baseline socio-demographic, clinical, biological and lifestyle factors associated with decline.

Results: 191 patients evaluated semi-annually were aviremic at all time points in the first 3 years; 166 had undergone CSF analysis. Viral presence in CSF was rare (10 /649 person-visits). Among the 191 patients, 23 (12%) declined cognitively over 3 years. In the multivariate analysis, the factors at baseline that met our threshold for predicting NC decline are listed in Table 1. Some risk factors identified in prior cross-sectional studies did not predict decline in this sample: older age, non-white ethnicity, low nadir CD4, CPE score, hepatitis C co-infection, diabetes, hypertension, low hemoglobin, low platelets, or a diagnosis of AIDS.

Risk Factor [Reference level]	Odds Ratio	95% Confidence interval
eGFR ≤ 50 mL/min [> 50]	6.80	1.35, 34.23
HIV infection ≥ 15 years [0-<5]	5.45	1.19, 25.02
Education ≤ 12 years [> 12]	4.25	1.45, 12.42
CSF protein >45 mg/dL [≤45]	3.25	1.13, 9.35

Table 1: Factors predicting NC decline over 36 months in aviremic HIV + people individuals in CHARTER

Conclusions: It is encouraging that cognitive decline over 3 years was uncommon in this sample of aviremic HIV+ individuals. The strongest predictor of decline was eGFR, a known independent predictor of atherosclerotic vascular disease. While an extension of this work in a larger sample will be needed to further clarify the contribution of vascular factors to cognitive decline in aviremic individuals, this work suggests that controlling additional cardio-vascular risk factors could be a useful strategy for minimizing cognitive decline. Modifiable risk factors were very common in the entire cohort, with as many as 80% reporting either smoking or a BMI ≥ 25. Smoking cessation and avoidance of obesity would be obvious starting points to maintain brain health.

470 Association Between Plasma Homocysteine Levels and Neuronal Injury in Untreated HIV

Erika Ahlgren[1]; Lars Hagberg[1]; Lars-Magnus Andersson[1]; Staffan Nilsson[2]; Dietmar Fuchs[3]; Henrik Zetterberg[1]; Magnus Gisslén[1]

[1]University of Gothenburg, Gothenburg, Sweden; [2]Chalmers University of Technology, Gothenburg, Sweden; [3]Innsbruck Medical University, Innsbruck, Austria

Background: Many HIV-1 infected patients without antiretroviral treatment suffer from neurological symptoms in a varying range of severity. Most patients with, and several without, neurological symptoms have elevated levels of neurofilament light protein (NFL) in cerebrospinal fluid (CSF), a marker of ongoing axonal injury. Hyperhomocysteinemia, related to vitamin B12 and folic acid deficiency, is associated with neurological symptoms. HIV-negative subjects with hyperhomocysteinemia and mild cognitive impairment show a significant reduction of brain atrophy in parts of the brain related to Alzheimer's disease when treated with vitamin B12.

The aim of this study was to investigate the correlation between homocysteine levels in plasma and signs of axonal injury in HIV-1 infected patients.

Methods: Homocysteine and B12-vitamin levels were analyzed in plasma with stable isotope dilution liquid chromatography tandem mass spectrometry (LC-MS/MS), and electrochemilluminescence immunoassay, respectively, from 80 neurological asymptomatic HIV-1 infected patients without antiretroviral treatment. NFL was measured, by an enzymatic 2-site quantitative immunoassay (UmanDiagnostics, Umea, Sweden), in CSF, and HIV RNA, neopterin and albumin in blood and CSF. 22 patients provided a second CSF and blood sample, in median 12.5 months, after antiretroviral treatment initiation.

Results: We found a significant correlation between the plasma level of homocysteine and CSF level of NFL in untreated patients, ($r = 0.52$, $p < 0.0001$). 20 patients had hyperhomocysteinemia (>15 μmol/L) and 20 had elevated levels of CSF NFL (age dependent). As expected, there was also a significant inverse correlation between homocysteine and B12 levels ($r = -0.41$. $p < 0.001$) but no significant correlation between B12 and CSF NFL. CSF neopterin correlated with CSF NFL ($r_s = 0.30$, $p = 0.008$) but not with serum homocysteine. In a multiple linear regression analysis homocysteine stood out as an independent predictor of CSF NFL in HIV-1 infected individuals. No significant difference was found in homocysteine levels before and after initiation of antiretroviral treatment.

Conclusions: A significant correlation was found between plasma homocysteine and CSF NFL levels in neurologically asymptomatic HIV-1 infected individuals without antiretroviral treatment. These data call for further research into the role of homocysteine or functional vitamin B12 deficiency in CNS injury in HIV-1 infected patients.

471 Plasma MicroRNA Profiling Predicts HIV-Associated Neurocognitive Disorder

Eugene L. Asahchop[1]; William G. Branton[1]; Segun M. Akinwumi[2]; Noshin Koenig[3]; Esther Fujiwara[2]; John Gill[3]; Christopher Power[1]

[1]University of Alberta, Edmoton, Canada; [2]University of Alberta, Edmonton, Canada; [3]Southern Alberta Clinic, Calgary, Canada

Background: HIV-associated neurocognitive disorder (HAND) is common, affecting 30-50% of HIV-infected patients despite the availability of effective antiretroviral therapy. The development of HAND is influenced by several factors including altered host and viral gene expression. Host-encoded microRNAs (miRNAs) regulate both host and viral gene expression. Thus, host miRNAs could contribute to the pathogenesis of HAND but also serve as biomarkers of diagnosis and prognosis as well as indicators of underlying disease mechanisms of HAND. Herein, we investigated plasma microRNA profiles among HIV/AIDS patients with and without HAND.

Methods: Plasma microRNAs was measured in age and sex-matched HAND (n=22) or nonHAND (n=25) patients (Cohort 1) by array hybridization (Affymetrix 3.0 miRNA genechip). Two software packages (Affymetrix Expression Console and Gene Spring) were used to normalize data and determine differentially expressed miRNAs. The median of each probeset in the HAND or nonHAND was calculated after normalization and differentially expressed miRNAs were identified. A second cohort (Cohort 2) consisting of prospectively recruited age- and sex-matched HAND (n=12) and nonHAND (n=12) patients was used to validate the miRNA profile in Cohort 1.

Results: Analyses of comparative expression identified 13 miRNAs in Cohort 1 that were up-regulated with a fold change (FC) of greater than 2 in the HAND group compared to the nonHAND group with one or both computational tools ($p<0.05$). Analysis of Cohort 2 confirmed up-regulation of 3 miRNAs identified in Cohort 1. In a univariate logistic regression analysis education level, CD4 and nadir CD4 T cell levels and these three miRNAs predicted HAND status based on *p*-values and odd ratios. Prediction of HAND status by

the individual miRNAs was more robust than that of CD4 nadir CD4 T cell levels. Bioinformatics analyses showed that these miRNAs were predicted to target genes involved in brain development, transcription, apoptosis of neural cells, and innate immune signaling.

Conclusions: Our findings revealed differential expression of three cell plasma-derived miRNAs in HAND versus nonHAND patients. These results suggest that plasma miRNAs might be used as biomarkers for HAND and also provide insights into the underlying disease mechanisms.

472 Performance of 4 Tools to Screen for HIV-Associated Cognitive Impairment

Judith Schouten[2]; Tanja Su[2]; **Rosan A. van Zoest**[1]; Ferdinand W. Wit[1]; Ineke G. Stolte[5]; Alan Winston[3]; Peter Reiss[1]; Peter Portegies[4]; Gert J. Geurtsen[2]; Ben A. Schmand[2]

[1]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands; [2]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [3]Imperial College London, London, Netherlands; [4]Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands; [5]Public Health Service of Amsterdam, Amsterdam, Netherlands

Background: A high prevalence of mild cognitive impairment (CI) has been reported in HIV-infected individuals on combination antiretroviral therapy (cART). An accurate screening tool would be useful to identify those at risk of HIV-associated CI who should undergo neuropsychological assessment (NPA). We assessed diagnostic characteristics of four often advocated screening tools: Mini Mental State Examination (MMSE), HIV Dementia Scale (HDS), Montreal Cognitive Assessment (MoCA), and a 3-item questionnaire published by Simioni et al (Simioni questionnaire).

Methods: Each screening tool and NPA were applied to a subset of HIV-uninfected and HIV-infected men on cART and with undetectable viremia ≥12 months participating in the AGE$_h$IV Cohort Study and enrolled in a nested cognitive substudy. Two methods were used to diagnose HIV-associated CI based on NPA outcomes: Frascati criteria as published by Antinori et al, and Multivariate Normative Comparison (MNC, comparing the cognitive profile of each HIV-infected individual with the overall cognitive profile of all HIV-negatives). Abnormal screening scores were defined by the following classical thresholds: MMSE ≤24/30, MoCA ≤25/30, HDS ≤10/16, HDS ≤14/16 and Simioni questionnaire ≥1/3 "yes, definitely". Diagnostic characteristics and receiver operating characteristic (ROC) analyses of screening tools were assessed using Frascati and MNC as the gold standards. Optimal thresholds were identified by calculating Youden index.

Results: HIV-positive and HIV-negative groups were highly comparable regarding age (median age: 54 years), sexual preference (92% MSM), educational level, subjective cognitive complaints, and depressive symptoms. HIV-infected men were infected for a median of 13.5 years and had undetectable viremia for a median of 8.3 years. Median nadir and current CD4-count were 170 and 625 cells/mm^3. None of the screening tools showed statistically significant between-group differences; sensitivity and specificity were moderate at best (see table). The ROC area under the curve of MMSE, HDS, and MoCA was 0.63, 0.61 and 0.71, and 0.70, 0.67 and 0.58 using Frascati and MNC as gold standard respectively. No large improvements in sensitivity or specificity were seen using optimal thresholds (see table).

	Results of screening tools (% below threshold)			Diagnostic characteristics of screening tools[2]			
	HIV-uninfected (n=74)	HIV-infected (n=103)	P-value[1]	Gold standard= CI as diagnosed by Frascati criteria[3]		Gold standard= CI as diagnosed by MNC[4]	
CLASSICAL THRESHOLDS				Sens	Spec	Sens	Spec
MMSE ≤24/30	0%	1%	1.00[a]	2%	100%	6%	100%
HDS ≤10/16	8%	4%	0.32[a]	6%	98%	6%	97%
HDS ≤14/16	50%	38%	0.11[b]	45%	69%	71%	69%
MoCA ≤25/30	11%	13%	0.71[b]	20%	94%	24%	90%
Simioni questionnaire ≥1/3	31%	30%	0.95[b]	35%	74%	41%	72%
OPTIMAL DISCRIMINATION THRESHOLDS							
MMSE (≤29/30 Frascati, ≤28/30 MNC)				67%	54%	59%	76%
HDS (≤13.5/16 Frascati, ≤14/16 MNC)				37%	81%	71%	69%
MoCA (≤27/30 Frascati, ≤25/30 MNC)				57%	74%	24%	90%

Abbreviations: CI, cognitive impairment; MNC, Multivariate Normative Comparison; Sens, sensitivity; Spec, specificity.
[1] Test type used: [a] Fisher's exact test, [b] Chi-square test.
[2] Diagnostic characteristics of screening tools were determined in the HIV-infected group (n=103).
[3] Frascati criteria identified CI in 48% of HIV-infected, but also in 36% of HIV-uninfected individuals (p=0.14).
[4] MNC identified CI in 17% of HIV-infected, and 5% of HIV-uninfected individuals (p=0.02).

Conclusions: Each of the four screening instruments performed poorly in detecting HIV-associated CI. Cognitive deficits in well-suppressed HIV infection are subtle, and no screening instrument so far seems optimal for use in clinical practice.

THURSDAY, FEBRUARY 26, 2015

Session P-G6 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Inflammation and Markers of Brain Injury in HAND

473 Astrocyte and Microglial Activation in Acute and Chronic HIV Pre- and Post-cART

Michael Peluso[1]; Victor G. Valcour[2]; Jintanat Ananworanich[3]; James L. Fletcher[4]; Somporn Tipsuk[4]; Bonnie Slike[3]; Nittaya Phanuphak[4]; Magnus Gisslén[5]; Henrik Zetterberg[5]; **Serena Spudich**[6]
RV254/SEARCH 010 & SEARCH 011 Study Teams

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [2]University of California San Francisco, San Francisco, CA, US; [3]Walter Reed Army Institute of Research, Bethesda, MD, US; [4]Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [5]University of Gothenburg, Gothenburg, Sweden; [6]Yale University, New Haven, CT, US

Background: Cerebrospinal fluid (CSF) YKL-40, a putative marker of astrocyte and microglial activation associated with Alzheimer's disease and multiple sclerosis, is a potentially useful biomarker of processes occurring within the central nervous system (CNS) of HIV-infected individuals. To explore the impact of early HIV infection and early versus later initiation of combination antiretroviral therapy (cART) on the CNS, we measured CSF YKL-40 in subjects with acute HIV infection (AHI) before and after initiation of cART and compared the results with individuals initiating cART during chronic HIV infection (CHI) and HIV-uninfected Thai controls.

Methods: AHI (n=33), CHI (n=34) and control (n=18) Thai subjects naïve to cART underwent blood and CSF sampling, followed by immediate cART initiation. CHI subjects met Thai criteria for initiating cART at baseline, having advanced disease typically with CD4 count <300. CSF was sampled at 24 (n=25) and 96 weeks (n=14) in the AHI and at 48 weeks

(n=10) in the CHI subjects, and HIV RNA levels and soluble biomarkers were measured at each visit. Cross-sectional analyses employed the Mann-Whitney and Spearman tests; paired analyses were used to compare subjects across time points.

Results: At initial sampling, median CD4 T cell count was 401 and 228 cells/uL in the AHI and CHI groups, respectively (p<0.0001). At baseline (median 18 days post estimated date of infection in AHI and unknown duration in CHI), median CSF YKL-40 was elevated in CHI (96,844 ng/L) compared with AHI subjects (80,754 ng/L; p=0.01) and controls (86,612 ng/L; p=0.07). In CHI but not AHI subjects, YKL-40 correlated with CSF neurofilament light chain (NFL; r=0.56, p<0.001), CSF neopterin (r=0.51, p=0.003), and CSF interferon-gamma-inducible protein 10 (IP-10; r=0.44, p=0.010). There were no correlations with HIV RNA or other soluble immune biomarkers in either group. After at ≥6 months of sustained cART (24 weeks in AHI and 48 weeks in CHI), the AHI group had a lower median CSF YKL-40 than CHI subjects (66,130 ng/L versus 87,414 ng/L, p=0.003).

Conclusions: Elevations in CSF YKL-40 suggestive of reactive astrocytes and microglial activation were present in CHI but not AHI subjects at baseline. YKL-40 declined after cART in CHI subjects, but remained elevated after treatment as compared to values in AHI participants after cART. YKL-40 correlation with NFL supports a role for astrocyte and/or microglial activation during CHI in neuronal injury that might be mitigated by early cART initiation.

474 CNS Immunoactivation and Neuronal Damage in Patients With Progressive Neurocognitive Impairment

Arvid Edén[1]; Donald Franklin[2]; Henrik Zetterberg[1]; Dietmar Fuchs[3]; Robert Heaton[2]; Scott Letendre[2]; Thomas Marcotte[2]; Richard Price[4]; Igor Grant[2]; Magnus Gisslén[1]

[1]University of Gothenburg, Gothenburg, Sweden; [2]University of California San Diego, San Diego, CA, US; [3]Innsbruck Medical University, Innsbruck, Austria; [4]University of California San Francisco, San Francisco, CA, US

Background: Although HIV-associated neurocognitive disorders (HAND) remain prevalent, the clinical significance is unclear. A recent report indicates a higher risk of symptomatic progression in subjects with asymptomatic neurocognitive impairment (ANI) than in unimpaired subjects. In a previous cross sectional analysis, we found that subjects with neurocognitive impairment (NCI) had increased cerebrospinal fluid (CSF) levels of neopterin but not neurofilament protein light subunit (NFL) compared to unimpaired subjects. Here, we investigated if a decline in neurocognitive performance (NP) was associated with ongoing neuronal damage measured by CSF NFL in a well characterized cohort of virally suppressed subjects.

Methods: Subjects on antiretroviral therapy (ART) with plasma HIV-1 RNA <50 c/ml without significant confounding conditions were identified from longitudinal studies (CHARTER and HNRC). Standardized NP testing was performed on two separate occasions. Subjects were classified as NP normal (NPN) or NCI (including subjects with ANI or mild neurocognitive disorder (MND)). According to NP test stability, subjects were categorized as NP stable or NP decline. CSF NFL was measured by enzymatic 2-site quantitative immunoassay (UmanDiagnostics, Umea, Sweden). CSF neopterin was measured by ELISA. The difference in CSF biomarkers between NCI and NPN were analyzed using a mixed effects model adjusting for age. Mann Whitney test was used to explore change in biomarkers according to NP progress. Correlations were explored using Pearson correlation.

Results: 100 (91% male) subjects were included in the analysis, 29 NPN and 71 with NCI (ANI=38; MND=33). 32 subjects (all in the NCI-group) had a NP decline from baseline to follow up. We found no differences in change of CSF NFL or neopterin in subjects with NP decline compared to NP stable subjects. However, the NCI-group had 17 % higher age-adjusted NFL (P=0.08) and 27 % higher neopterin (P=0.03) compared to the NPN-group. Neopterin was significantly correlated with NFL in the NCI-group (r=0.38; P=0.001), but not in the NPN-group (R=-0.17; P=0.4).

Conclusions: We did not find any difference in CSF NFL or neopterin in virologically suppressed subjects with progressive neurocognitive impairment compared to subjects without functional decline. However, the correlation found between CSF neopterin and NFL in subjects with NCI indicates an association between immune activation, neuronal damage and neurocognitive impairment that needs to be further characterized.

475 Endothelial Function and CNS Measures in Primary HIV Infection Pre and Post Early ART

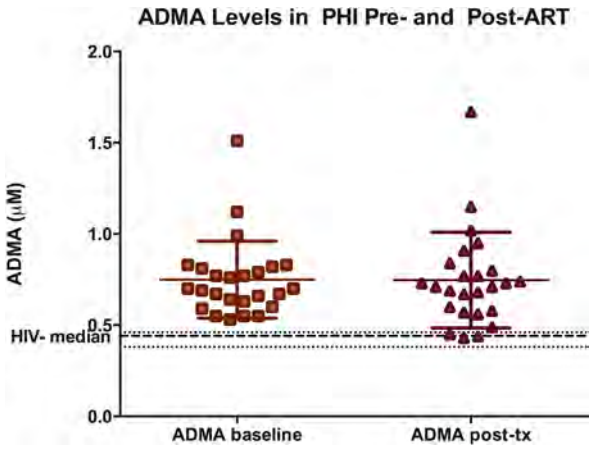
Sebastian Urday[1]; **Zaina Zayyad**[1]; Julia Peterson[2]; Felicia C. Chow[2]; Kevin R. Robertson[3]; Richard Price[2]; Priscilla Hsue[2]; Serena Spudich[1]

[1]Yale University, New Haven, CT, US; [2]University of California San Francisco, San Francisco, CA, US; [3]University of North Carolina, Chapel Hill, NC, US

Background: HIV infection, vascular perturbation, and central nervous system (CNS) dysfunction may associate through common pathogenic pathways of inflammation observed even in antiretroviral therapy (ART)-controlled HIV infection. We examined plasma levels of asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor and biomarker of endothelial dysfunction in participants recruited during primary HIV infection (PHI, < 365 days post infection, DPI), examining associations between ADMA and measures of systemic and CNS perturbation before and after ART and over time.

Methods: 25 ART-naïve PHI individuals were assessed at baseline and at an interval 6-12 months after initiating ART. Assessments included clinical blood measures, an 11 test neuropsychological battery (summarized as total Z and 4 test NPZ-4), and CSF total white blood cell count and albumin ratio. ADMA levels in PHI subjects were compared with published values in HIV-uninfected controls (HIV-, n=50) and chronically infected subjects (median 13 years duration infection) with viral suppression on ART (n=148) measured in the same laboratory. Nonparametric statistics were employed for analysis.

Results: PHI subjects were assessed at baseline at median 139 (IQR 54, 182) DPI and subsequently at median 281 (202, 372.5) days after ART initiated 256 (133, 744) DPI. At baseline, PHI participants had higher median ADMA 0.70 (0.62, 0.82) μM than historical HIV- (0.44 μM, 0.38, 0.46) and chronically HIV-infected subjects on ART (0.46 μM, 0.41, 0.52, p < 0.0001 for each comparison). ADMA levels in PHI did not change from baseline to post-ART (p=0.87), and remained elevated compared with HIV- and chronic, on-ART comparisons (p<0.0001 for each). In PHI, ADMA did not associate with total Z or NPZ4 pre- or post-ART, nor correlate over time with respect to change in each measure. Of laboratory measures, pre-ART ADMA associated with blood CD8+ T cell count (p=0.05), as previously reported in chronic infection.



Conclusions: At baseline, PHI subjects had ADMA levels higher than values from uninfected and chronically infected ART-treated historical comparisons, and ADMA elevation correlated with levels of blood CD8+ T cells, but not CNS measures. In contrast to prior findings in cross sectional studies of treated, suppressed chronic HIV subjects, ADMA levels in our subjects did not change after more than 9 months on ART initiated during early infection, suggesting ongoing endothelial dysfunction.

476 Platelet-Endothelial Interactions in SIV-Associated CNS Disease

Claire E. Lyons[2]; Hannah Schneider[3]; Liz Engle[1]; Suzanne E. Queen[1]; Craig N. Morrell[4]; Joseph L. Mankowski[1]; **Kelly A. Pate**[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Tufts University, North Grafton, MA, US; [3]Colorado State University, Fort Collins, CO, US; [4]University of Rochester, Rochester, NY, US

Background: Platelet decline is associated with increased risk for the development of HIV-associated neurocognitive deficits. Interaction of activated platelets with brain microvascular endothelium may contribute to platelet decline and directly influence the permeability of the blood brain barrier. We sought to determine whether these interactions occur in the SIV-infected pigtailed macaque model of HIV-associated CNS disease.

Methods: SIV-infected macaques and mock-inoculated controls (N=4) were euthanized and perfused to clear the organs of blood during acute (N=6) or terminal (N=10) infection. Immunohistochemistry for resident (CD68) and non-resident (CD163, Mac387) macrophages, SIV (KK41) and platelets (CD42b) was used to visualize platelet-endothelial interactions in the brain and perivascular macrophage infiltrates characteristic of CNS disease. Platelet rich plasma was harvested during terminal infection (N = 10) and from mock inoculated controls (N=6). Platelets were stimulated with the thromboxane agonist U46619 then assayed for surface expression of the activation marker p-selectin using flow cytometry. Confluent monolayers of brain microvascular endothelial cells (BMECs) were exposed to washed platelets from SIV infected macaques (N=5), uninfected macaques (N=6) or media alone in transwells and permeability quantified with FITC-inulin.

Results: Brains from SIV-infected macaques were more likely than brains from uninfected controls to have platelets bound to vascular endothelium during acute (RR 4.0, P=0.03) and terminal (RR 3.6, P=0.04) infection. 6 of the 10 SIV+ macaques had CNS disease during terminal infection and resident Mac387+ (RR 3.4, P=0.0001) or CD163+ macrophages (RR 1.44, P=0.0005) but not non-resident CD68+ macrophages (RR 1.2, P=0.2) were observed in these animals with increased likelihood around platelet-lined vessels. SIV-infected macrophages were similarly observed with increased likelihood around platelet-lined vessels (RR 1.5, P=0.007). Platelets harvested from infected macaques with CNS disease demonstrated more activation from U46619 stimulation (91.1%) than macaques without CNS disease (15.7%, P=0.036). Permeability of BMECs decreased two-fold following incubation with platelets from SIV infected macaques compared with uninfected macaques (P=0.01).

Conclusions: Activated platelet-endothelial interactions may represent a protective mechanism against development of macrophage infiltrates in CNS disease that is removed in the context of HIV-associated thrombocytopenia.

477 Microbial Translocation Is Associated With Neuroinflammation in HIV Subjects on ART

Jaime H. Vera[1]; Qi Guo[2]; Adriano Boasso[1]; Louise Greathead[1]; James Cole[1]; Courtney Bishop[2]; Rabiner Ilan[2]; Roger Gunn[2]; Paul Matthews[1]; Alan Winston[1]

[1]Imperial College London, London, United Kingdom; [2]Imanova Centre for Imaging Sciences, London, United Kingdom

Background: Circulating microbial products such as bacterial 16s ribosomal DNA have been associated with immune activation in otherwise effectively treated HIV-infected subjects. The impact of microbial translocation on cerebral parameters remains unknown. The aim of this study was to examine the relationship between a marker of microbial translocation and brain biomarkers of inflammation, function and structure in treated HIV-infected individuals

Methods: Plasma bacterial 16s ribosomal DNA (r16s DNA) was measured by quantitative polymerase chain reaction (qPCR) in 12 neurologically asymptomatic HIV-infected subjects on ART (viral load <50 copies/mL). All subjects underwent the following investigations: cerebral PET CT imaging assessing neuroinflammation using the 18kDA translocator protein (TSPO) radioligand [^{11}C]PBR28, diffusion tensor imaging (DTI) for the evaluation of white matter integrity and a lumbar puncture for the analysis of cerebrospinal fluid (CSF) chemokines. Relationships between plasma r16s DNA and [^{11}C]PBR28 binding, DTI fractional anisotropy (FA) and mean diffusivity (MD) and CSF chemokines were explored by correlation analyses

Results: Median (range) for age and CD4 count were 41(26-49) years and 645(350-1240) cells/uL, respectively. Plasma r16s DNA median(range) was 4.2(41-2) copies/mL. Significant associations between increase concentration of plasma r16s DNA and greater [^{11}C]PBR28 binding were observed across several brain regions (Table 1). r16s DNA was also associated with greater MD in the forceps major (r=0.532; *P*=0.07), right inferior longitudinal fasciculus (r=0.601; *P*=0.03) and right inferior fronto-occipital fasciculus (r=0.509; *P*=0.09). Finally, r16s DNA level was positively correlated with the proinflammatory chemokine IL-8 in the CSF (r=0.599; *P*=0.024, CI=0.152 to 0.956)

Table 1. Correlation coefficients (r) between [^{11}C] PBR28 binding and plasma r16s DNA

Biomarker	Basal ganglia	Globus pallidus	Temporal lobe	Parietal lobe	Occipital lobe	Caudate	Striatum	Medulla	Midbrain
Plasma Ribosomal 16s DNA (copies/mL)	0.881*	0.928*	0.818*	0.832*	0.861*	0.877*	0.871*	0.645*	0.811*

[Legend Table 5.1: **P<0.05, ** P<0.1]*

Conclusions: In neuroasymptomatic treated HIV-infected individuals microbial translocation is associated with markers of neuroinflammation and abnormalities in white matter integrity. The potential contribution of microbial translocation to the pathogenesis of HIV-associated cognitive impairment warrants further investigation.

478 DKK1 Is Associated With HIV-Associated Neurocognitive Impairment

Chunjiang Yu[1]; Melanie Seaton[1]; Scott Letendre[2]; Robert Heaton[2]; **Lena Al-Harthi**[1]

[1]Rush University Medical Center, Chicago, IL, US; [2]University of California at San Diego, San Diego, CA, US

Background: DKK1 is a soluble antagonist of the Wnt/β-catenin pathway. It binds to LRP5/6 (a co-receptor of Wnts) and sequesters it away from Wnts. We demonstrated that Wnt/β-catenin is a critical regulator of the glutamate/glutamine cycle in astrocytes, and diminished Wnt/β-catenin signaling perturbs their neuroprotective properties. As a consequence, we hypothesized that increased DKK1 would increase the risk for neurocognitive impairment (NCI) in an HIV-infected (HIV+) cohort.

Methods: To assess the relationship between plasma DKK-1 and NCI, blood plasma samples from 41 HIV+ and 43 HIV- adults were obtained from the UCSD TMARC cohort. DKK1 and MCP-1 plasma levels were measured by immunoassay. MCP-1 was included as a comparison marker; it is a neuroinflammatory chemokine driving monocyte/macrophage infiltration into the brain. All subjects were assessed using a standardized comprehensive NC battery that adhered to Frascati guidelines. NC performance was summarized using the global deficit score (GDS) method.

Results: Levels of MCP-1 (p = 0.02) but not DKK1 (p = 0.65) were higher in HIV+ subjects than in HIV- subjects. Among HIV+ subjects, higher levels of DKK-1 (d=0.63, p = 0.05) but not MCP-1 (p = 0.59) were associated with NCI. The association between DKK1 and NCI strengthened when recursive partitioning was used to identify an informative threshold value in DKK1: among the 41 HIV+ subjects, those who had plasma DKK1 levels of at least 1,129 pg/ml had a 6.0-fold increased odds of having NCI (75% vs 33%, 2-tail FET p=0.04). The effect size was large and the association between DKK1 and NCI was highly specific (92%), although the sensitivity was poor (35%). In comparison, recursive partitioning failed to identify a statistically significant threshold value for MCP-1. Multivariable analysis among HIV+ subjects identified that the association between higher DKK1 levels and NCI remained statistically significant after accounting for the effects of nadir CD4+ T-cell counts, drugs of abuse, and ART use.

Conclusions: These findings underscore the potential specificity of DKK1 as a biomarker for NCI in HIV+ adults. Based on our prior work, the mechanism driving this relationship is via HIV and inflammatory responses that mediate elevation in DKK1 which in turn reduces Wnt/β-catenin signaling in astrocytes and diminish glutamate/glutamine cycling by astrocytes, leading to neurotoxicity.

479 Markers of HIV-Associated Cognitive Impairment Are Elevated in HIV-Infected Patients With Neurosyphilis

Emily Ho; Lauren Tantalo; Sharon Sahi; Trudy Jones; Shelia Dunaway; Christina Marra
University of Washington, Seattle, WA, US

Background: Despite combination antiretroviral therapy (cART), cognitive impairment is common in HIV-infected patients. Compared to those without cognitive impairment, cerebrospinal fluid (CSF) concentrations of IP-10, MCP-1, neurofilament light chain (Nfl) are higher in cognitively impaired HIV-infected patients. Blood concentrations of activated monocytes are also higher in HIV-infected patients with dementia. Cognitive impairment may be more common in HIV-infected patients with past syphilis. The goal of this study was to determine if markers of HIV-associated cognitive impairment were higher in HIV-infected patients with neurosyphilis.

Methods: Banked frozen CSF and cryopreserved CSF cells and peripheral blood mononuclear cells (PBMCs) were collected from 109 individuals: 48% HIV-infected (72% on cART), 95% men, 76% Caucasian; 64% early syphilis; 35 had neurosyphilis (reactive CSF-Venereal Disease Research Laboratory [VDRL]), 74 had uncomplicated syphilis (syphilis; CSF white blood cells [WBCs] ≤5/ul, nonreactive CSF-VDRL). CSF concentrations of HIV RNA were measured by RT-PCR; MCP-1, IP-10 were measured by multiplex assay (Mesoscale Discovery), Nfl by ELISA, % activated monocytes (coexpressing CD14 and CD16) by flow cytometry. Differences between groups were assessed by Mann-Whitney U test. The influence of covariates was assessed using linear regression.

Results: The results in the four groups are shown in the Table. Among the groups with syphilis and with neurosyphilis, CSF IP-10 concentrations were higher in the HIV-infected patients than in the HIV-uninfected patients. Among patients with syphilis, CSF NFL was higher in the HIV-infected patients than the HIV-uninfected patients, but CSF NFL did not differ between the neurosyphilis patients. Among patients with HIV, CSF HIV RNA, IP-10 and MCP1; and blood % activated monocytes were higher in those with NS than in those with syphilis. Taking into account CSF WBCs, CSF IP-10 but not MCP1, HIV RNA or blood activated monoctyes remained significantly higher in HIV-infected patients with neurosyphilis than in HIV-infected patients with syphilis (P<0.001).

Median (# patients)	HIV negative Syphilis (n=41)	HIV positive Syphilis (n=33)	P value	HIV negative Neurosyphilis (n=16)	HIV positive Neurosyphilis (n= 19)	P value	P value*
CSF HIV RNA (cpm)		75 (n=18)			929 (n=12)		0.049
IP10 (pg/ml)	1204 (n=33)	2530 (n=32)	0.001	4669 (n=14)	13965 (n=15)	0.04	<0.001
MCP1 (pg/ml)	286 (n=33)	337 (n=32)	NS	366 (n=15)	519 (n=15)	NS	0.009
NFL (ng/ml)	156 (n=37)	345 (n=33)	0.001	302 (n=16)	529 (n=18)	NS	NS
CSF % activated monocytes	5.9 (n=19)	3.0 (n=21)	NS	1.8 (n=4)	1.2 (n=10)	NS	NS
Blood % activated monocytes	6.3 (n=17)	5.4 (n=22)	NS	8.9 (n=3)	19.9 (n=7)	NS	0.001

NS = not statistically significant
*comparison between HIV positive Syphilis and HIV positive Neurosyphilis groups

Table: Markers of HIV-associated Cognitive Impairment in the Patient Groups

Conclusions: Compared to HIV-infected patients with syphilis and patients with neurosyphilis alone, HIV-infected patients with neurosyphilis have higher concentrations of CSF and peripheral blood biomarkers that are associated with cognitive impairment. These studies suggest that patients with concomitant HIV and neurosyphilis may be at higher risk of cognitive impairment.

480 CD14+ PBMC Secrete Cytokines Linked to HIV-Associated Neurocognitive Disorders

Melissa A. Agsalda-Garcia[4]; Victor G. Valcour[1]; Pasiri Sithinamsuwan[2]; Guangxiang G. Zhang[4]; Cecilia M. Shikuma[4]; James L. Fletcher[3]; Nicholas Hutchings[1]; Alexandra Schuetz[5]; Jintanat Ananworanich[3]; Bruce Shiramizu[4]
[1]*University of California San Francisco, San Francisco, CA, US;* [2]*Phramongkutklao Hospital, Bangkok, Thailand;* [3]*The Thai Red Cross AIDS Research Centre, Bangkok, Thailand;* [4]*University of Hawaii, John A. Burns School of Medicine, Honolulu, HI, US;* [5]*Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand*

Background: HIV-associated neurocognitive disorders (HAND) persist despite the availability of combined antiretroviral therapy (cART) and believed to be at least partially the consequence of mechanisms associated with monocytes. In addition to transporting HIV into the brain, monocytes secrete pro-inflammatory cytokines that lead to neuronal damage. In this study, we analyzed cytokines that were secreted from CD14-selected peripheral blood mononuclear cells (PBMC) from HIV-infected individuals with HAND and normal cognition (NC) at baseline (cART naïve) and after one year on cART to determine which cytokines were associated with HAND.

Methods: The study population consisted of 61 HIV-infected Thais who were enrolled in SEARCH011 (NCT00782808); 28 diagnosed with HAND and 33 with NC at entry. PBMC were collected at baseline and 12 months post cART initiation. CD14+ PBMC were separated by magnetic beads and cultured overnight (median 91.4% purity by flow cytometry). Cytokine secretions were measured from the supernatants captured after 24 hour culture and using a custom 10-plex Milliplex MAP kit detecting fractalkine, IFN-g, IL-2, IL-4, IL-6, IL-8, IL-10, IP-10, MCP-1, and TNF-α. HIV DNA copies were also analyzed from the CD14+ PBMC using a real-time qPCR. Non-parametric Spearman correlation and Wilcoxon rank-sum test were conducted.

Results: Of the cytokines analyzed, only IL-8 and MCP-1 levels were significantly higher in those with HAND in comparison to NC at baseline (p<0.003). HIV DNA levels were directly correlated to IL-8 (r=0.33; p=0.01) and MCP-1 (r=0.39; p=0.003) at baseline but not after one year.

Conclusions: This study demonstrated that individuals with HAND experience continued inflammation and the type of cytokine supports monocyte involvement consistent with their likely role as viral reservoirs that continue to persist despite cART. High levels of IL-8 and MCP-1 continued to be secreted by CD14+ PBMC in individuals with HAND despite initiation of cART. We hypothesize that secretion of these cytokines may play an important role in promoting the continued transmigration of monocytes into the brain that leads to the persistence of HAND despite cART.

481 MBL-HIV1gp120 Immunoreactivity Is Associated With Markers of Neuronal Injury

Carmen Teodorof[1]; Damhnien Nguyen[1]; Nishi Kadakia[1]; Ricky Maung[2]; Benchawanna Soontornniyomkij[1]; Cristian Achim[1]; David Moore[1]; Eliezer Masliah[1]; Marcus Kaul[2]; Kumud Singh[1]
[1]University of California San Diego, San Diego, CA, US; [2]The Sanford Burnham Medical Research Institute, La Jolla, CA, US

Background: Mannose-binding lectin (MBL), an innate immune response protein binds directly to the mannose residues on HIV-1 envelope glycoprotein 120 (gp120) via its carbohydrate recognition domain (CRD) and leads to complement activation and virus opsonization. We hypothesized that MBL-gp120 interactions in HIV-1 infected brain will be associated with neuronal damage.

Methods: HIV-1 infected frontal cortex brain tissues with or without HIV encephalitis (HIVE) (obtained from California NeuroAIDS Tissue Consortium) and hemi-brain sections from wild type (WT) and gp120 transgenic (gp120tg) mice were used to analyze MBL expression and immunoreactivity with somatodendritic marker MAP2, neurodegeneration marker phospho-Tau (pTau), synaptic marker synaptophysin (SYN) and complement activation product C3d. Furthermore, human primary neuronal cultures (HPNs) were treated with 5nM IIIB-gp120 to determine its effects on neuronal damage. Immunohistochemistry, confocal microscopy, z stacking and immunoblotting were used to analyze expression and immunoreactivity of MBL and gp120 with neuronal markers.

Results: Presence of immune complexes (ICs) of MBL and gp120 was associated with a loss of neuronal dendrites (MAP2) and SYN puncta; and an increase of pTau immunoreactivity in HIVE vs. non-HIVE brain (N=5 each). Furthermore, complement activation product C3d was associated with immunodeposition of MBL-gp120 ICs in HIVE tissue. In a gp120tg mouse model, MBL isoforms MBL1 and MBL2 formed ICs with gp120; and compared to the WT mice, hemi-brains from gp120tg mice showed a loss of neuronal dendrites (MAP2) and SYN suggesting MBL-gp120 mediated neuronal damage. Also, 5nM IIIB-gp120 treatment of human primary neurons (HPNs) showed clear immunostaining of MBL-gp120 in perinuclear vesicles and MAP2 along neuronal processes within 30min, followed by a loss of MAP2 and SYN, and an increase of pTau by 6hrs. Confocal microscopy orthogonal view via z-stacking and immunoblots clearly confirmed the immunoreactivity of MBL and gp120.

Conclusions: Presence of MBL-gp120 immune complexes was associated with a loss of MAP2 and SYN, and in an increase of pTau and C3d in HIV-1 infected brain, gp120tg mouse model and HPN cultures suggesting a unique role of MBL-gp120 interactions and complement activation in neuronal damage.

WEDNESDAY, FEBRUARY 25, 2015

Session P-G7 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Aging and Cognitive Decline

482 Amyloid Uptake by PET Imaging in Older HIV+ Individuals With Cognitive Impairment

Ned Sacktor; Richard Skolasky; Heidi Roosa; Yun Zhou; Weiguo Ye; Noble George; Dean Wong; Mona Mohamed
Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: Cognitive impairment among older HIV+ individuals could be due to HIV itself, vascular disease, or the early onset of Alzheimer's disease. Amyloid deposition, a hallmark of Alzheimer's, can be detected by brain position emission tomography (PET) imaging. A previous PET study using another marker of amyloid, [^{11}C] Pittsburgh B compound (PIB), in 16 HIV+ subjects (age: mean(SD) =46(3) years) with normal cognition (69%) and HIV-associated neurocognitive disorder (HAND) (31%) did not show increased [^{11}C] PIB uptake. The objective of this study was to determine whether abnormal amyloid deposits measured by PET [^{18}F] AV-45 is present in older HIV+ individuals > age 50 years, and is increased in HIV+ individuals with symptomatic HAND (mild neurocognitive disorder (MND) and dementia), compared to asymptomatic HAND [asymptomatic neurocognitive impairment (ANI)] and normal cognition).

Methods: 25 HIV+ individuals (age: mean(SD) = 60.8(6.0) years) received neurological evaluations including neuropsychological testing, functional assessments and high resolution research tomography (HRRT) PET [^{18}F] AV-45 imaging. 6 HIV- individuals [age: mean(SD) = 68.3(7.8)] received similar assessments. AV-45 uptake was measured by cerebellum standardized uptake value ratios (SUVR) in 17 cortical and subcortical regions, and compared 1) between HIV+ individuals with and without symptomatic HAND, and 2) by HIV serostatus using the Wilcoxon test. Qualitative analysis of an abnormal PET scan was also performed.

Results: HAND stage for HIV+ individuals was as follows: normal cognition-3, ANI-8, MND-7, HIV dementia-6. 12% of the HIV+ individuals (age range 57-64 years) had increased AV-45 uptake by qualitative analysis. HIV+ individuals with symptomatic HAND (MND and dementia) had increased AV-45 uptake in the hippocampus [median(IQR)= 1.26(1.10-1.35)] and basal ganglia [median(IQR)= 1.64 (1.39-1.76)], compared to HIV+ individuals with ANI/normal cognition [hippocampus median(IQR) = 1.07(1.03-1.16)], (p= 0.049) and basal ganglia [median(IQR) =1.49(1.41-1.52), (p= 0.049). There were no differences in regional uptake by HIV serostatus though HIV- individuals were older than HIV+ individuals (p= 0.015).

Conclusions: Amyloid deposition is increased in a minority of HIV+ individuals > age 50. Amyloid deposition in HIV+ individuals with symptomatic HAND is increased compared to individuals with asymptomatic HAND or normal cognition in specific regions which could account for cognitive impairment.

483 Lower CSF Amyloid-β Levels Are Associated With Worse Neurocognitive Functioning in HIV-Infected Adults With a Family History of Dementia

Pariya L. Fazeli[1]; David J. Moore[1]; Donald Franklin[1]; Robert Heaton[1]; Christina Marra[2]; Benjamin B. Gelman[3]; Allen McCutchan[1]; Igor Grant[1]; Scott Letendre[1]
[1]University of California San Diego, San Diego, CA, US; [2]University of Washington Seattle, Seattle, WA, US; [3]University of Texas Medical Branch, Galveston, TX, US

Background: Studies of HIV-infected (HIV+) patients have shown that independently both family history of dementia (FHD) and lower levels of Aβ-42 are associated with worse neurocognitive functioning. We measured cerebrospinal fluid (CSF) levels of Aβ-42 in a convenience sample of 184 HIV+ adults currently on antiretroviral therapy (ART) (90 with FHD and 94 demographically-matched without FHD) and examined the relationship between these variables and HIV-associated neurocognitive disorders (HAND).

Methods: All participants underwent comprehensive neuropsychological and neuromedical assessments, and determination of CSF concentration of Aβ-42. FHD was defined as a self-reported first or second-degree relative with a dementia diagnosis. Univariate analyses were used to determine whether HAND status was associated with FHD, CSF Aβ-42, or any potential covariates (e.g., demographics, HIV disease characteristics) and to examine if CSF Aβ-42 levels differed by FHD. Multivariable logistic regressions then examined the association of CSF Aβ-42, FHD, and their interaction on HAND.

Results: FHD did not differ between those with and without HAND ($p = 0.24$); however, CSF Aβ-42 levels were significantly ($p = 0.03$) lower in the HAND group. Further, CSF Aβ-42 was not associated with FHD ($p = 0.89$). Multivariable models controlling for race and comorbidity rating showed a significant main effect of CSF Aβ-42 ($p = 0.03$) and a trend ($p = 0.06$) towards an interaction between FHD and CSF Aβ-42, such that lower CSF Aβ-42 was only associated with HAND in those with FHD ($p < 0.01$) as compared to those

without FHD ($p = 0.83$). Examining inheritance type (maternal vs. paternal), type of dementia (AD vs. non-AD), or number of relatives with a dementia diagnosis did not strengthen these associations. A median split was conducted on raw CSF Aβ-42 values to create high and low CSF Aβ-42 groups and showed that those with low CSF Aβ-42 and FHD had the highest prevalence of HAND (74%), while the remaining groups were similar (high CSF Aβ-42 FHD: 49%; high CSF Aβ-42 no FHD: 52%; low CSF Aβ-42 no FHD: 57%). Post-hoc analyses showed that the CSF Aβ-42 X FHD interaction trend was driven by speed of information processing ($p = 0.01$).

Conclusions: FHD moderates the effect of CSF Aβ-42 on HAND. These findings highlight the complexities of analysis of biomarkers of age-related neurodegeneration in HAND.

484 Cystatin C Is Associated With Neurocognitive Impairment in Older HIV+ Adults

Marissa Sakoda[1]; Pariya L. Fazeli[2]; Scott Letendre[2]; Dilip Jeste[2]; Igor Grant[2]; David J. Moore[2]

[1]John A. Burns School of Medicine at the University of Hawaii, Honolulu, HI, US; [2]University of California San Diego, San Diego, CA, US

Background: The incidence and prevalence of HIV infection among older adults is on the rise. Older age appears to increase the risk of neurocognitive impairment (NCI) among HIV+ adults. Understanding the correlates of NCI in older HIV+ adults is important, particularly biomarkers in readily accessible body fluids. Among older HIV- adults, elevated cystatin C predicts neurocognitive (NC) decline and mortality. Cystatin C is elevated in HIV+ persons, but the association of cystatin C and NCI has yet to be studied. Our goal was to examine differences in cystatin C between HIV+ and HIV- older adults, and, within the HIV+ adults, to examine the association of cystatin C with NCI.

Methods: Participants were 77 HIV+ and 47 HIV- older adults (50 years or older) enrolled in a cross-sectional study at UCSD's HIV Neurobehavioral Research Program. HIV+ participants were taking suppressive antiretroviral therapy. Cystatin C was measured in blood plasma by immunoassay. A standardized comprehensive neurocognitive assessment was performed. NCI was based on domain and global deficit scores derived from demographically corrected T-scores.

Results: The HIV+ group had a significantly higher cystatin C concentration than the HIV- group ($p<0.001$). In the HIV+ group, higher cystatin C levels were associated with NCI (d=0.42, p=0.0549) and were not statistically significant in the HIV- group (d=0.12, p=0.70). Recursive partitioning identified that HIV+ subjects who had cystatin C levels ≥ 0.75 mg/L had a 79% increased relative risk of NCI (p=0.02). In a multivariable model that included relevant covariates (e.g., gender, race, depression), higher cystatin C levels remained associated with NCI (p=0.02).

Conclusions: HIV+ adults had higher cystatin C concentrations than HIV- adults, consistent with prior reports. Higher plasma cystatin C was associated with NCI in older HIV+ adults but not in HIV- adults. Cystatin C may be a useful clinical biomarker to identify HIV-infected persons at increased risk for NCI. A significant limitation of the present study is the cross-sectional design. Future projects should investigate the role of cystatin C in neurocognitive decline over time among older persons living with HIV.

485 Leptomeningeal Enhancement on MRI in the Aging HIV-Positive Population

Bryan R. Smith[1]; Sally Steinbach[1]; Govind Nair[1]; Caryn Morse[1]; Joseph Snow[2]; Suad Kapetanovick[2]; Henry Masur[1]; Avindra Nath[1]; Daniel S. Reich[1]

[1]National Institutes of Health, Bethesda, MD, US; [2]National Institute of Mental Health, Bethesda, MD, US; [3]National Institutes of Health, Clinical Center, Bethesda, MD, US

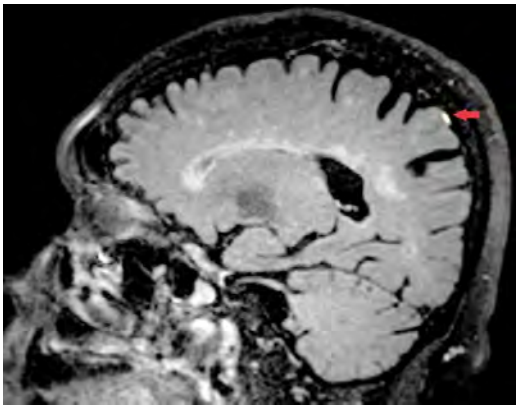
Background: HIV infection is associated with neurologic sequelae that may be related to chronic CNS inflammation despite treatment with antiretroviral therapy (ART). Objective biomarkers of CNS involvement with HIV infection are needed to identify patients at risk of neurologic complications. Leptomeningeal contrast-enhancing lesions on MRI have been described recently in multiple sclerosis, a neuro-inflammatory disorder, where they correspond pathologically to perivascular lymphocytic and mononuclear infiltration of the leptomeninges. However, such foci have not been described in the HIV-positive population. This study explored the prevalence of leptomeningeal contrast-enhancing lesions in the HIV-positive population and possible clinical correlations.

Methods: Brain MRI, using an optimized 3D post-contrast T2-weighted fluid-attenuated inversion recovery (FLAIR) technique, was collected in 51 HIV-positive and 10 HIV-negative participants in a cross-sectional study of HIV and cognition. Expert raters evaluated focal gadolinium enhancement in the leptomeningeal compartment.

Results: Focal contrast enhancement was detected in the leptomeningeal compartment in 13/51 HIV-positive cases (25%) vs. 0/10 HIV-negative cases (0%; p=0.07). Demographics (age, race, sex) and clinically relevant medical variables (systolic blood pressure, c-reactive protein values, diabetes mellitus and chronic hepatitis C status) were similar between HIV-positive and HIV-negative groups. All HIV-positive participants were receiving ART, and 50/51 had a plasma HIV viral load <40 copies/ml at the time of evaluation.

Within the HIV-positive group, advanced age was the only clinical factor associated with leptomeningeal enhancement (p = 0.029). HIV-positive participants with leptomeningeal enhancement had a mean age of 55.3 yrs compared to 49.1 yrs in participants without enhancement. There was no correlation with CD4 cell count, CD4 nadir, duration of HIV infection, or history of neurologic disorders.

Conclusions: A subset of HIV-positive individuals on ART have contrast-enhancing multifocal lesions in the leptomeningeal compartment on MRI. This finding is more common with advanced age. Longitudinal studies are needed to identify whether this novel imaging technique has prognostic significance in older HIV-positive individuals.



Sagittal MRI 3D post-contrast fluid-attenuated inverse recovery (FLAIR) image of an HIV-positive patient demonstrating a leptomeningeal contrast-enhancing lesion (arrow).

Conclusions: A subset of HIV-positive individuals on ART have contrast-enhancing multifocal lesions in the leptomeningeal compartment on MRI. This finding is more common with advanced age. Longitudinal studies are needed to identify whether this novel imaging technique has prognostic significance in older HIV-positive individuals.

486 Hepatitis C Infection and Cognition in Older HIV+ Adults: Data From the Center of Excellence on Disparities in HIV and Aging (CEDHA)

Oluwatoyin M. Adeyemi[1]; Sue Leurgans[2]; Alan Landay[2]; David Bennett[2]; Lisa Barnes[2]

[1]Ruth M Rothstein CORE Center, Cook County Health and Hospitals System, Chicago, IL, US; [2]Rush University Medical Center, Chicago, IL, US

Background: Neurocognitive impairment in patients with controlled HIV is well reported. Chronic hepatitis C (HCV) has also been associated with poor neurocognitive and neuropsychiatric outcomes. We sought to evaluate the impact of HCV co-infection on neurocognition and quality of life (QOL) among older adults with well controlled HIV infection enrolled in CEDHA.

Methods: Data come from CEDHA, a prospective study of older adults with and without HIV living in Chicago, IL. The current analysis included 166 HIV+ persons (mean age = 58 (±5.5) yrs; 124 (74.7%) male, 69% black) without active drug or alcohol use who completed a structured clinical evaluation including a battery of 19 cognitive tests and 3 quality of life questions. Cognitive data included composite measures of global cognition and five different cognitive domains: episodic memory, semantic memory, working memory, perceptual speed and visuospatial ability. Linear regression models were used to examine the relationship between HCV infection and neurocognition, and logistic regression models were used to examine the association of HCV with quality of life.

Results: The mean education of participants was 13.1 (±2.8) years and the mean CD4 was 621(±286) cells/mm; 97.0% had undetectable HIVRNA. Sixty-four persons (38.6%) were HCV+ and were more likely to be black (OR=2.8, p=0.009) and have lower education 12.1yrs vs 13.8yrs (p<0.0001) when compared with HCV- participants. In linear regression models that controlled for age, sex, education, and race, HCV infection was significantly associated with lower global cognition, episodic memory, and perceptual speed. In models that further adjusted for nadir CD4 count, only the association with episodic memory remained. In logistic regression models adjusted for the same terms, HCV infection was related to fair/poor self-rated health, after controlling for nadir CD4 count (OR=3.1, p=0.004).

Conclusions: HCV infection is associated with poorer episodic memory and QOL rating in patients with well controlled HIV. These impairments may have adverse effects on adherence and other long term outcomes in HIV patients. The effect of HCV direct acting antivirals on these outcomes needs further exploration.

487 Neurocognitive Screening Tests Are Associated With Cardiovascular Risk and VACS Scores

Andrea Calcagno[1]; Marielisabetta Scarvaglieri[1]; Daniela Vai[2]; Alessandro Livelli[2]; Letizia Marinaro[1]; Giancarlo Orofino[2]; Nicole Pagani[1]; Daniele Imperiale[2]; Giovanni Di Perri[1]; Stefano Bonora[1]

[1]University of Torino, Torino, Italy; [2]ASLTO2, Torino, Italy; [3]ASLTO2, Torino, Italy

Background: HIV-associated neurocognitive disorders (HAND) are still highly prevalent despite effective antiretroviral treatment; several associated factors have been identified including cardio- e cerebrovascular risk factors. Despite the recommendation to perform screening neurocognitive (NC) tests in all HIV-positive patients there is still uncertainty regarding the optimal tools as well as the selection criteria.

Methods: In adult HIV-positive patients cardiovascular risk assessment [5-year D:A:D (DAD5) and 10-year Progetto Cuore (Cuore10) risk scores], mortality risk (VACS-index) as well as screening NC tests (IHDS, Clock Drawing Test, Frontal Assessment Battery) were performed. Patients with IHDS below 10 received a full NC testing by a trained neuropsychologist. Data are expressed as average (± standard deviation, SD) and parametric tests were used for all analysis (Pearson's test for continuous variables).

Results: 441 patients (78% male, 95.4% Caucasian) were enrolled. Age, BMI and eCRCL were 48 years (±11.5), 24.8 kg/m^2 (±4.1) and 81.9 ml/min (±19.5) respectively. Average current and nadir CD4 were 538 cell/uL (±309) and 219 (±177); out of 407 patients on treatment (91.7%), 289 (71%) showed HIV RNA below 50 copies/mL.

Average DAD5 and Cuore10 were 3.2% (±3.8%) and 5.5% (±9%) and respectively 3.9% and 5.1% of patients fell in the high-risk strata (>10% and >20%, respectively). VACS index was 27.5 (±16.9). Average IHDS, Clock and FAB scores were 10.6 (±1.3), 1.28 (±1.25), 15.4 (±2); they were abnormal in 87/422 (20.6%), 88/354 (24.9%) and 13/101 patients (12.9%) respectively. IHDS scores were associated with clock (r=-0.15, p=0.007) and FAB scores (r=0.583, p<0.001); they were also significantly associated with VACS (r=-0.417, p<0.001), DAD5 (r=-0.333, p<0.001) and Cuore10 (r=-0.276, p<0.001) risk scores. With increasing DAD5 risk profiles patients presented higher prevalence of altered IHDS: 14.1% (low risk), 32.7% (intermediate risk) and 57.1% (high risk). Similar results were observed with Cuore10 risk strata (both for IHDS and FAB tests).

Conclusions: A significant proportion of HIV-positive efficaciously treated patients present altered neurocognitive screening tests (12.9% to 24.9%); this prevalence increases significantly in patients with high cardiovascular risk (28.6% to 57.1%). Beyond supporting the possible influence of cardio- and cerebrovascular abnormalities in HAND, these data suggest to screen for neurocognitive disorders patients with high cardiovascular risk profile.

488 Aerobic Exercise Attenuates Cognitive Decline and Brain Volume Loss Associated With HIV

Brian Basco[1]; Mario Ortega[1]; Jodi M. Heaps[3]; Laurie Baker[2]; Florin Vaida[4]; Beau Ances[1]

[1]Washington University School of Medicine, St. Louis, MO, US; [2]University of Missouri St. Louis, St. Louis, MO, US; [3]Missouri Institute of Mental Health, St. Louis, MO, US; [4]University of California San Diego, San Diego, CA, US

Background: HIV infected (HIV+) individuals are now reaching an advanced age, through stable treatment with highly active anti-retroviral therapy (HAART). However, HIV and aging are still risk factors for cognitive decline and neuropathologic deterioration seen in magnetic resonance imaging (MRI). Healthy lifestyle factors such as regular exercise may provide benefits to HIV+ individuals. Few studies have shown definitive benefit of aerobic exercise (AE) to HIV+ cognitive status, and none have used MRI. In this study we determine if a history of AE is beneficial to brain integrity and neurocognitive test scores in a cohort of HIV+ individuals.

Methods: A cross-sectional cohort of 70 HIV+ individuals (19-82 age range) had neuropsychological performance (NP) testing, neuroimaging, and completed an extensive self-report AE questionnaire that split the cohort into physically active (n=22) and sedentary (n=48) groups. Student's t-tests were used to analyze demographics. Analysis of variance (ANOVA) was used to study main effects of exercise on a brief NP battery, which consisted of the following tests: Trail Making Tests A and B, Hopkins Verbal Learning Test, Digit-Symbol Coding, F-A-S and Verbal Fluency. NP tests were grouped by executive and motor function for analysis. ANOVAs were also used to study the effects of exercise upon brain volumes. This included brain volumes affected by HIV, such as the caudate and putamen, regions affected by exercise, such as the hippocampus, and general brain regions like total gray and total white matter

Results: Active and sedentary HIV+ individuals were similar for age, sex, education, and laboratory values. Physically active HIV+ patients performed significantly better than sedentary HIV+ participants on NP tests of executive (p=.04, mean Z scores of -0.654 and -0.956 respectively, [95% CI, 0.27, 0.72]) but not motor function (p=.13, mean Z scores of -0.331 and -0.827, respectively). Additionally, physically active HIV+ individuals had a significantly larger putamen (p=0.028) across the lifespan compared to the sedentary cohort.

Conclusions: Across a range of ages, AE may maintain healthy brain volumetrics in HIV+ individuals and led to improved cognitive performance. Future studies should consider exercise as an adjunctive therapy to HAART for HIV+ individuals.

489 The Impact of Physical Activity on Cognition in Men With and Without HIV

Anne Monroe[1]; Long Zhang[7]; Lisa P. Jacobson[7]; Todd T. Brown[1]; Michael Plankey[4]; Eric Miller[3]; James T. Becker[5]; Eileen Martin[6]; Ned Sacktor[1]
On behalf of the Multicenter AIDS Cohort Study

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]University of California Los Angeles, Los Angeles, CA, US; [4]Georgetown University, Washington, DC, US; [5]University of Pittsburgh, Pittsburgh, PA, US; [6]Rush University Medical Center, Chicago, IL, US; [7]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

Background: HIV-associated neurocognitive disorder (HAND) is a highly prevalent complication of HIV infection, however, the mechanism of its development and its optimal treatments are only partially understood. Our objective was to determine the association between physical activity and cognitive function and the effect of HIV on that association among participants from the Multicenter AIDS Cohort Study (MACS).

Methods: The International Physical Activity Questionnaire (IPAQ) short form was administered during a semiannual MACS visit occuring from April 1, 2010 to March 31, 2011, serving as the baseline visit for this analysis. Metabolic Equivalents (METs) total score and categorical physical activity scores (low, moderate, and high) were generated. Assessments of psychomotor function (Symbol Digit Modalities Test (SDMT)), executive functioning (Trail Making Test Part B), and motor speed (Trail Making Test Part A) were performed at the baseline visit and at up to eight subsequent MACS visits. We determined the association between median test scores and physical activity, demographic, and clinical factors at the baseline visit and also examined the association between demographic and clinical factors and the change in test performance over time.

Results: Of the 622 men included, 44% were HIV-infected. Low, moderate, and high activity was reported in 19%, 31% and 50% of the HIV-uninfected men and 28%, 25%, and 48% of the HIV-infected men, respectively. HIV was not significantly associated with SDMT, Trails A, or Trails B score in multivariate analysis. In the cross-sectional analysis, high physical activity category was associated with better SDMT and Trails B test scores compared with low activity (β=0.45, p=0.02 and β=0.45, p=0.03) among all men and was associated with better SDMT scores when HIV-infected men were examined separately (β=0.57, p=0.01). In the longitudinal analysis, physical activity category at baseline was not associated with subsequent change in SDMT, Trails A, or Trails B.

Conclusions: Higher physical activity category was associated with better scores on tests of psychomotor and executive functioning in a cohort of HIV-infected and –uninfected men at baseline but did not affect the change over time. Physical activity may have protective effects against cognitive impairments, independent of HIV status.

490 Abnormal Lung Function Associated With Abnormal Brain Structure and Function in HIV

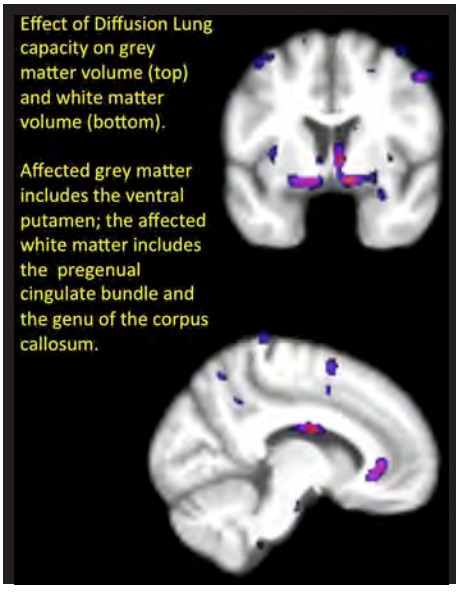
Alison Morris[1]; Lawrence Kingsley[1]; **Matthew Gingo**[1]; Meghan Fitzpatrick[1]; Roger Detels[3]; Oto Martinez[3]; Eric Miller[3]; Jeffrey Alger[3]; Eric Kleerup[3]; James T. Becker[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]University of Pittsburgh, Pittsburgh, PA, US; [3]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US

Background: Cognitive deficits and alterations in brain structure are associated with chronic obstructive pulmonary disease. Both cognitive impairment and chronic obstructive pulmonary disease are non-AIDS-associated comorbidities that are increased in HIV-infected individuals, but whether lung function abnormalities have an additional impact on brain function in HIV is unknown. The purpose of this study was to determine the relationships among lung function, brain structure at the voxel level, and cognitive function and to determine whether these relationships are altered in HIV infection.

Methods: 65 men participating in the Multicenter AIDS Cohort Study (55% HIV-infected) underwent measurement of lung function, brain structural magnetic resonance imaging, and neuropsychological testing. Pre-and post-bronchodilator spirometry and measurement of diffusion capacity of the lung for carbon monoxide (DLCO) were performed in accordance with American Thoracic Society standards. Standard reference equations for predicted values were used for spirometry and DLCO; DLCO was corrected for hemoglobin and carboxyhemoglobin. Three-dimensional anatomical brain images were segmented by tissue type, and the whole brain gray matter analyzed using Voxel-Based Morphometry. Multivariate models were constructed in Statistical Parametric Mapping (SPM8) to examine the impact of HIV and lung function on brain volume measured at the voxel level. The statistical threshold was set at p<.005 and 100 voxels.

Results: The associations between DLCO and brain structure are shown in Figure 1 overlaid onto the MACS MRI template (MRIcron); the affected Grey Matter included the ventral putamen including the basal forebrain, and the affected White Matter included the pregenual part of the cingulum. Linear regression analyses found no significant interactions between lung function, smoking and HIV in predicting GM volume of the ventral putamen. Lower diffusion capacity was associated with a worse cognitive summary score (Beta=.37, p=.005), independent of HIV infection (Beta=.11).



Conclusions: We report here, for the first time, on the relationship between lung function impairment and abnormal brain structure. In addition, we report on the relationship between these lung function and cognition in this group of study participants

491 HIV DNA and Neurocognitive Impairment in Older Subjects on Suppressive ART

Michelli Faria de Oliveira[1]; Ben Murrell[1]; Josué Pérez-Santiago[1]; Milenka Vargas[1]; Ronald J. Ellis[2]; Scott Letendre[2]; Igor Grant[2]; Davey M. Smith[1]; Steven P. Woods[2]; Sara Gianella[1]
[1]University of California San Diego, La Jolla, CA, US; [2]HIV Neurobehavioral Research Center, San Diego, CA, US

Background: Older adults are at high risk for HIV-associated neurocognitive impairment (NCI), but the underlying neurobiological mechanisms of this heightened risk are poorly understood.

Methods: This study included 18 younger (22-40 years) and 26 older (50-71 years) chronically HIV+ subjects on suppressive ART. Subjects were characterized for NC functioning by Global Deficit Score (GDS) using a standardized battery consistent with Frascati recommendations for neuroAIDS. Levels of HIV DNA were measured in PBMC by droplet digital PCR, soluble markers of monocyte and general immune activation (sCD14, sCD163, MCP-1, IL-6, IL-8, TNF-a, IP-10 and Neopterin) were measured in blood and cerebrospinal fluid (CSF) by immunoassay. Associations between GDS and other variables were evaluated by regression analysis adjusted for estimated duration of infection (EDI) and age. Mann Whitney tests were used to detect differences between groups.

Results: Sixteen (36.4%) subjects had NCI (GDS ≥0.5). GDS was not associated with current or nadir CD4 in either age group (p>0.5). Stepwise regression with AIC model selection starting with a model containing all identified predictors of GDS retained only age group (young vs old) and HIV DNA, with a significant interaction between age group and HIV DNA (p=0.022). In the younger group, no association was found between GDS and HIV DNA levels (r=-0.08, p>0.5). For older subjects, higher levels of HIV DNA were associated with GDS (r=0.57, p=0.003), which remained significant after adjusting for EDI and age. Higher HIV DNA levels were specifically associated with deficits in executive functions among older individuals (p= 0.004), while no differences were found for other abilities in either age group. Higher levels of IL-8 in blood plasma were associated with worse GDS among older subjects after adjusting for age (p=0.04), but not for the younger subjects. No associations were found between GDS and the other markers.

Conclusions: Prior studies have linked the HIV DNA reservoir size to NCI and our findings identify that this association is strongest in HIV+ adults older than 50, along with IL-8, which we have previously linked to evidence of inflammation on brain magnetic resonance spectroscopy. These findings add to emerging evidence that the correlates of NCI differ in older and younger HIV+ adults, which supports tailoring therapy based on age. In addition, our findings suggest that interventions aiming to reduce the HIV DNA reservoir may impact the central nervous system.

492 Suppressive ART Is Key to Reduce Neurocognitive Impairment in Aging HIV+ Individuals

Christina C. Yek[1]; David M. Smith[1]; Gabriel Wagner[1]; Susan Morgello[2]; Scott Letendre[1]; Igor Grant[1]; Sergei L. Kosakovsky Pond[1]; Sara Gianella[1]
On behalf of the CHARTER group
[1]University of California San Diego, San Diego, CA, US; [2]Icahn School of Medicine at Mount Sinai, New York, NY, US

Background: Little is known about how the HIV reservoir behaves and how it affects neurocognitive function as infected individuals age. Here, we evaluate these outcomes in a cohort of aging, chronically-infected individuals.

Methods: CHARTER participants who were ≥45 years old, reported continual antiretroviral therapy (ART) use, and had ≥4 years of follow-up were studied (n=36). Neurocognitive assessments and biannual plasma viral loads were measured for all subjects. Longitudinal samples were available for 28 subjects. DNA was extracted from blood using a PAXgene Blood DNA Kit. Droplet digital PCR was performed using primers for total HIV DNA (*pol*), 2-LTR circles and RPP30 (for normalization). Deep sequencing of partial envelope (*env*), *gag* and reverse transcriptase (RT) regions was done using a Roche 454 FLX Titanium instrument. Phylogenetic and mutational spectra analyses were performed using a HIV-specific bioinformatics pipeline.

Results: Subjects were divided into suppressed (<50 copies/ml with ≤1 blip, blip ≤200copies/ml [n=15]), partially-suppressed (<50 copies/ml for >50% time points with consecutive blips [n=12]) and non-suppressed groups (n=9). Suppressed subjects had lower HIV DNA levels (p=0.0002), 2-LTR circle copies (p=0.002) and *env* diversity (p=0.03) than non-suppressed subjects. In cross-sectional analysis, older age was associated with decreased HIV DNA (p=0.005), decreased *env* and RT diversity (p=0.05 and 0.03, respectively), and decreased frequency of drug resistance-associated mutations in RT (DRAMs) (p=0.03) in suppressed subjects. In longitudinal analysis, *env* diversity decreased with time (p=0.002) and HIV DNA did not change among suppressed subjects, whereas HIV DNA increased (p=0.004) with no change in *env* diversity among the non-suppressed. Finally, subjects with neurocognitive impairment (NCI) were more likely to be partially- or non-suppressed (p=0.04) and have no DRAMs (p=0.05).

Conclusions: In a cohort of aging chronically-infected individuals, suppressive ART was associated with decreased viral reservoir size, genetic diversity and less frequent drug resistance, consistent with sustained control of HIV infection. Furthermore, we found that DRAMs correlated with better neurocognitive performance, reflecting reduced fitness and therefore neurovirulence of these viral strains. Our findings suggest that continual suppressive therapy is necessary to control viral replication and reduce the incidence of HIV-associated neurocognitive disease in older individuals.

493 Mixed Membership Trajectory Model of Cognitive Impairment in the MACS

Samantha A. Molsberry[1]; Fabrizio Lecci[2]; Brian Junker[2]; Sandra Reynolds[3]; Andrew Levine[4]; Eileen Martin[5]; Cynthia A. Munro[6]; Ned Sacktor[6]; James T. Becker[1]; Neuropyschology Working Group O. Multicenter AIDS Cohort Study[7]
[1]University of Pittsburgh, Boston, MA, US; [2]Carnegie Mellon University, Pittsburgh, PA, US; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [4]University of California Los Angeles, Los Angeles, CA, US; [5]Rush University Medical Center, Chicago, IL, US; [6]Johns Hopkins University School of Medicine, Baltimore, MD, US; [7]National Institutes of Health (NIH), Bethesda, MD, US

Background: In spite of known risk factors for cognitive impairment in HIV Disease, the trajectories that individuals may take from a state of normal cognition to HIV-associated dementia are unknown. We applied a novel statistical methodology to identify: trajectories to cognitive impairment, and factors that affected the "closeness" of an individual to one of the canonical trajectories

Methods: The Multicenter AIDS Cohort Study (MACS) is a four-site longitudinal study of the natural and treated history of HIV Disease among gay and bisexual men. Using data from 3,892 men (both HIV-infected and uninfected) enrolled in the neuropsychology substudy of the MACS, a Mixed Membership Trajectory Model (MMTM) was applied to capture the pathways from normal cognitive function to mild impairment to severe impairment. MMTMs allow the data to identify canonical pathways and to model the effects of risk factors on an individual's "closeness" to these trajectories.

Results: We identified three canonical trajectories - a "normal aging" profile with relatively low probability of even mild impairment until well into middle age (60% of sample), a "premature aging" profile with a probability of mild impairment climbing at age 45-50 (21% of sample); and, an "unhealthy" profile with a high probability of mild impairment even at a very young age (19% of sample). The premature aging profile was characterized as including men who were from the original study cohort (1984-1991), had HIV Disease and had AIDS, with 11% with HCV infection. The unhealthy profile was characterized by men from the latest enrollment cohort (2001-2003), HCV infection, and other medical confounds. We tested the effects of seven time invariant predictors on the "closeness" of individuals to each of these profiles. HCV infection, HIV, AIDS, recruitment cohort, confounding conditions, depression, and the interaction between cohort and race have a significant effect on the closeness of individuals to these profiles.

Conclusions: We have invoked, for the first time, a novel, data driven method for identifying trajectories to cognitive impairment in men with, or at-risk for HIV infection. These results provide new insights into the natural and treated history of HIV/AIDS and suggest that premature cognitive impairment remains a concern, particularly for those individuals infected with HIV who develop AIDS.

494 Brain Structural Correlates of Trajectories to Cognitive Impairment in HIV Disease

James T. Becker[1]; Mikhail Popov[1]; Samantha A. Molsberry[1]; Fabrizio Lecci[2]; Brian Junker[2]; Sandra Reynolds[3]; Eric Miller[4]; Cynthia A. Munro[5]; Ann Ragin[6]; Ned Sacktor[5]

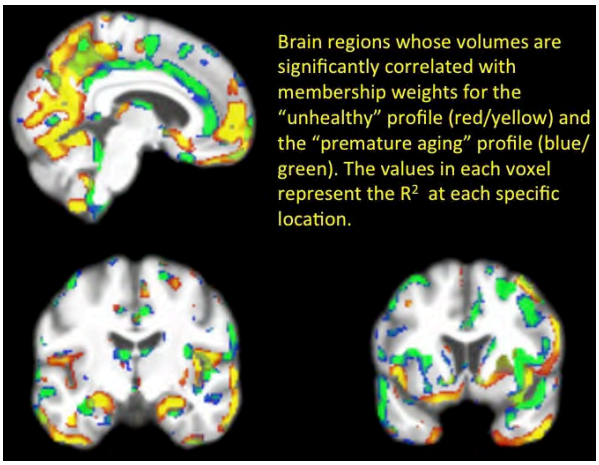
[1]University of Pittsburgh, Pittsburgh, PA, US; [2]Carnegie Mellon University, Pittsburgh, PA, US; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [4]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US; [5]Johns Hopkins University School of Medicine, Baltimore, MD, US; [6]Northwestern University, Feinberg School of Medicine, Chicago, IL, US

Background: We have described trajectories to mild/severe cognitive impairment among participants in the MultiCenter AIDS Cohort Study (MACS). The goal of this analysis was to determine the relationship between patterns of brain atrophy and membership weights in the individual trajectories among men with brain MRI scans.

Methods: A total of 293 (160 HIV-infected; mean age = 55.9 yrs.; mean education: 16.4 yrs.) of the men enrolled in the MACS MRI study contributed data to this analysis. We used voxel-based morphometry (in SPM8) to segment the brain images into gray matter (GM), white matter and CSF volumes. The analysis used smoothed (8x8x8 mm FWHM) GM images.

The trajectory model was created using data from 3,892 MACS participants and had identified three trajectories - a "normal aging" profile with relatively low probability of even mild impairment until well into middle age, a "premature aging" profile with a probability of mild impairment climbing at age 45-50; and, an "unhealthy" profile with a high probability of mild impairment even at a very young age. Each study participant had a membership weight for each of these trajectories. Because these weights are parameter estimates, we used multiple imputation methodology to account for the uncertainty in memberships weights in the correlation analyses. We estimated model parameters with SPM8 for 100 imputations, manually performed the post-hoc contrasts, and pooled the results accounting for between– and within–imputation variability.

Results: The results of the analyses (as R^2) are shown in Figure 1. The areas colored in Red/Yellow are those whose volume is associated with the membership weight for the "unhealthy" profile; those in Blue/Green are associated with the "premature aging" profile. The unhealthy profile is linked to areas associated with cognitive decline, including the posterior cingulate/precuneus, the hippocampus, and the inferior frontal cortex. Premature aging membership weights are linked to the cingulate gyrus, the insula, and the basal ganglia.



Conclusions: Trajectories to cognitive impairment in HIV disease are the result, in part, of atrophy in brain regions linked to HIV disease (basal ganglia), as well as cortical regions linked with normal and pathological aging. These data suggest the possibility of predicting cognitive morbidity based on patterns of CNS atrophy.

495 Cognitive Reserve and Neuropsychological Functioning in Older HIV-Infected People

Benedetta Milanini[1]; Nicoletta Ciccarelli[1]; Silio Limiti[1]; Pierfrancesco Grima[2]; Massimiliano Fabbiani[1]; Barbara Rossetti[3]; Elena Visconti[1]; Enrica Tamburrini[1]; Roberto Cauda[1]; Simona Di Giambenedetto[1]

[1]Institute of Infectious Diseases, Catholic University of Sacred Hearth, Rome, Italy; [2]Division of Infectious Diseases, "S. Caterina Novella" Hospital, Galatina, Italy; [3]Division of Infectious Diseases, University of Siena, Italy

Background: Progress in treatments has led to HIV-infected patients getting older. Both age and HIV are risk factors for cognitive decline. We explored the role of cognitive reserve (CR) to the maintenance of neuropsychological integrity in older HIV-infected people.

Methods: We performed a multicenter study, consecutively enrolling asymptomatic HIV+ patients ≥60 years old during routine outpatients visits. A comprehensive neuropsychological battery (exploring learning, attention, fine motor skills, language and working memory) was administered. All participants also underwent the TIB, an Italian version of the National Adult Reading Test, which is correlated with the Intelligence Quotient (IQ), and the Cognitive Reserve Index (CRI) questionnaire, which includes three sections: education, working activity and leisure time. For each cognitive test, raw scores were transformed into Z-scores; cognitive impairment was defined according to Frascati criteria. Relationships between TIB, CRI and cognitive performance were investigated by logistic or linear regression analyses.

Results: Fifty patients [86% males, median age 66 years (range 60-83), 12% HCV co-infected, 4% past IDU, 24% with past AIDS-defining events, 30% affected by diabetes, median CD4 cells count 570/μL (IQR 465-747), median nadir CD4 cells count 104/μL (IQR 50-239), all on cART (40% on NNRTI and 60% on PI) and with HIV-RNA<50copies/mL] were enrolled. Nineteen patients (38%) showed an Asymptomatic Neurocognitive Impairment (ANI). Median CRI and TIB scores were 114 (IQR 98-134) and 113 (IQR 105-116), respectively; these two measures resulted significantly correlated (r_s=0.70; p<0.001).

At logistic regression analysis, only CRI (OR 0.95; 95% CI 0.91-0.98; p=0.004) and TIB (OR 0.81; 95% CI 0.71-0.92; p=0.001) were associated with a lower risk of ANI. Higher CRI and TIB were significantly correlated with a better performance (medium Z-score) both globally and at each cognitive domain, except for working memory; for this domain, diabetes was the only variable associated with a worse performance (B -0.39; 95% CI -0.73; -0.50; p=0.025) after adjusting for previous cardiovascular events (B -0.24; 95% CI -0.55; -0.76; p=0.134).

Conclusions: Our findings highlight the role of IQ and CR over clinical variables in the maintaining of cognitive integrity in a virologically-suppressed older HIV-infected population. A lifestyle characterized by intellectual and social nature leisure activities may help to cope aging and HIV-related neurodegeneration.

THURSDAY, FEBRUARY 26, 2015

Session P-G8 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Mitochondrial Dysfunction in HAND and Depression

496 Mitochondrial DNA, Neurologic and Systemic Inflammation, and Immune Dysregulation

Josué Pérez-Santiago; Michelli Faria de Oliveira; Susanna R. Var; Steven P. Woods; Sara Gianella Weibel; Sanjay Mehta; Ben Murrell; Tyler R. Day; Ronald J. Ellis

University of California San Diego, La Jolla, CA, US

Background: We recently found that higher levels of cell-free mtDNA in cerebrospinal fluid (CSF) were associated with more neurological and systemic inflammation in a clinically heterogeneous cohort of HIV infected individuals. Here we investigated how CSF mtDNA levels relate to inflammation and immune status in a cohort of virologically suppressed individuals, and in 5 individuals following structured treatment interruption (STI).

Methods: Using droplet digital PCR, we quantified cell-free mtDNA levels from the CSF supernatant in 41 HIV-infected individuals with completely suppressed HIV RNA levels in CSF and blood plasma (<50 copies/mL), and in five HIV infected individuals who underwent STI. For each CSF and plasma sample, we also measured markers of inflammation and cellular trafficking (IP-10, MCP-1, IL-6, IL-8, TNF-α, MIP-1α and sCD14). Statistical analyses were performed in R statistical software.

Results: Levels of mtDNA in CSF supernatant were significantly higher in individuals with a diagnosis of AIDS when compared to participants without AIDS (median: 6.34 $\log_{10}$ copies/mL versus 3.81 $\log_{10}$ copies/mL, p=0.0003). Using fixed-effects regression analyses, higher levels of mtDNA in CSF were also associated with lower $CD4^+$ T-cell nadir (r=-0.43, p=0.004). Furthermore, higher levels of mtDNA in CSF were associated with more inflammation in CSF as measured by MCP-1 (r=0.56, p=0.0002), TNF-α (r=0.73, p=0.01), and in blood plasma measured by IL-8 (r=0.44, p=0.004) and TNF-α (r=0.43, p=0.005). In a multivariate analysis, higher levels of mtDNA remained significantly associated with higher levels of MCP-1 (p=0.03) and TNF-α (p=0.01) in CSF when adjusted for AIDS status. In subjects undergoing STI, mtDNA levels in CSF rebounded prior to CSF and blood plasma HIV RNA and prior to pleocytosis in all individuals. Furthermore, pleocytosis was associated with both levels of mtDNA (p=0.03) and HIV RNA in CSF (p=0.01) when evaluated in a multivariate mixed-effects model.

Conclusions: In virologically suppressed individuals, higher levels of mtDNA in CSF were strongly associated with more neurologic and systemic inflammation, and with a lower CD4+ nadir and AIDS status. Also after STI, mtDNA levels rose prior to HIV rebound and pleocytosis in CSF. These results suggest that increased levels of cell-free mtDNA in CSF play a role in neuro-inflammation especially in individuals with more advanced HIV disease. Our data provide important insights to the pathophysiology of immune dysregulation in the CNS during AIDS.

497 CSF Metabolomics Implicate Bioenergetic Adaptation as a Neural Mechanism Regulating Shifts in the Cognitive States of HIV-Infected Subjects

Norman J. Haughey[1]; Alex DIckens[1]; Reena Deutsch[2]; Michelle Mielke[3]; Timothy Claridge[4]; Igor Grant[2]; Thomas Marcotte[2]; Scott Letendre[2]; Justin McArthur[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]University of California San Diego, San Diego, CA, US; [3]Mayo Clinic, Rochester, MN, US; [4]University of Oxford, Oxford, United Kingdom

Background: Although combinational antiretroviral therapy (ART) has been an effective tool in controlling replication of the Human Immunodeficiency Virus (HIV), ART has not been completely effective to suppress neurological complications. While some cases of cognitive impairment can be attributed to ART failure, many individuals develop HIV-Associated Neurocognitive Disorders (HAND) with stable ART, little or no detectable viral load, and CD4 counts in the normal range. HIV-infection and ART are each associated with disturbances in peripheral and central bioenergetics. Although brain imaging studies have shown the importance of metabolic abnormalities in HAND, the underlying bioenergetic pathways modified by infection and ART are not well understood.

Methods: The metabolic composition of CSF was analysed using ^{1}H-NMR spectroscopy, which focused on energy metabolites. Metabolic biomarkers for cognitive states were identified using multivariate PLS regression modelling of the acquired spectra, combined with non-parametric analyses of metabolites with clinical features.

Results: Multivariate modeling and cross-validated recursive partitioning identified several energy metabolites that, when combined with clinical variables, classified subjects based on change in neurocognitive states. Prognostic identification for worsening was achieved with 4 features that included 1 clinical measure (no change in a detectable plasma viral load), and 3 metabolites (elevated citrate and acetate; decreased creatine), to produce a model with a predictive accuracy of 92%, sensitivity of 88%, and 96% specificity. Prognosis for improvement contained 7 features that included 2 clinical measures (first visit age <47 years, new or continued use of antiretrovirals), and 5 metabolites (elevated glutamine and glucose; decreased *myo*-inositol, b-glucose, and creatinine) to generate a model with a predictive accuracy of 92%, sensitivity of 100% and specificity of 84%.

Conclusions: These CSF metabolic results suggest that worsening cognitive status in HIV-infected patients is associated with increased aerobic glycolysis, and improvements in cognitive status are associated with a shift to anaerobic glycolysis. Dietary, lifestyle and pharmacologic interventions that promote anaerobic glycolysis may protect the brain in setting of HIV infection with ART.

498 Altered Monoamine and Acylcarnitine Metabolites in HIV Patients with Depression

Edana Cassol[1]; Vikas Misra[2]; Susan Morgello[3]; Gregory D. Kirk[4]; Shruti H. Mehta[4]; Dana H. Gabuzda[2]

[1]Carleton University, Ottawa, Canada; [2]Dana-Farber Cancer Institute, Boston, MA, US; [3]Mount Sinai Hospital, New York, NY, US; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

Background: Depression is a frequent comorbidity in HIV infection and an important predictor of poor treatment outcomes and increased mortality. Accumulating evidence suggests that inflammation and increased tryptophan catabolism are associated with increased risk of developing major depressive disorder in HIV infection, but the mechanisms leading to depression remain poorly understood.

Methods: The severity of depressive symptoms was assessed by Beck Depression Inventory or Center for Epidemiological Studies Depression Scale. Untargeted metabolomic profiling of plasma from 104 subjects across three independent cohorts (32 HIV+ subjects on ART from NNTC and CHARTER [median CD4 288 cells/ul, median plasma VL 50 copies/ml; n=15 and n=17 with and without depressive symptoms], 36 HIV+ [median CD4 350 cells/ul, median plasma VL 630 copies/ml; n=13 and n=23 with and without depressive symptoms] and 36 HIV- [n=12 and n=24 with and without depressive symptoms] subjects from ALIVE) was performed using liquid or gas chromatography followed by mass spectrometry to detect > 400 metabolites. Cytokine profiling was performed by Bioplex array. Bioinformatic analysis were performed in Metaboanalyst and R.

Results: Decreased monoamine metabolites of phenylalanine/tyrosine catabolism (phenylacetate and 4-hydroxyphenylacetate) and acylcarnitines (propionylcarnitine, isobutyrylcarnitine, isovalerylcarnitine, and 2-methylbutyrylcarnitine) in plasma distinguished between subjects with and without depressive symptoms in both HIV+ and HIV- cohorts (FC>1.2, p<0.05, FDR<10%), and these alterations correlated with the severity of depression. In HIV+ subjects, depressive symptoms were associated with augmented IFN responses (IFN-gamma, CXCL9, CXCL10) and tryptophan catabolism (increased kynurenine to tryptophan ratio), and these changes correlated with metabolite alterations associated with depression (p<0.05, FDR<10%). Altered metabolites mapped to pathways involved in monoamine metabolism, mitochondrial function, and inflammation,

suggesting a model in which complex inter-relationships between monoamine metabolism and mitochondrial bioenergetics contribute to biological mechanisms involved in depression that may be augmented by inflammation during HIV infection.

Conclusions: Integrated approaches targeting inflammation, monoamine metabolism (tryptophan [serotonin], phenylalanine [dopamine], and trace amines), and mitochondrial pathways may be important for prevention and treatment of depression in people with and without HIV.

499 Mitochondrial Injury and Cognitive Function in HIV Infection and Methamphetamine

Susanna R. Var; Tyler R. Day; Andrej Vitomirov; Davey M. Smith; Virawudh Soontornniyomkij; Cristian L. Achim; Sanjay Mehta; Josué Pérez-Santiago
University of California San Diego, San Diego, CA, US

Background: Mitochondria carry their genome and are critical in providing energy for cellular processes in the central nervous system (CNS). Damage to mitochondrial DNA (mtDNA) is associated with many neurodegenerative diseases. HIV infection and methamphetamine (METH) abuse, a common comorbidity, can cause damage to mtDNA and subsequently lead to neurocognitive morbidity. Here we evaluated the role of mitochondrial injury in relation to HIV infection and METH use.

Methods: We collected brain tissue of parietal and frontal lobes from HIV-infected individuals with evidence of METH use (n=6), HIV-infected individuals with no METH use (n=4) and HIV-negative controls (n=7) from the National NeuroAids Tissue Consortium. DNA was extracted from gray and white matter from each lobe. We quantified mtDNA levels and mitochondria carrying the "common deletion" as a measurement of mitochondrial injury in relation to a cellular control using droplet digital PCR (ddPCR). Measures of mtDNA and "common deletion" were evaluated in relation to clinical Global Deficiency Score and other clinical variables.

Results: Our examination of all groups together found that levels of "common deletion" increased with age in the parietal white (r=0.75, p=0.0005) and grey matter (r=0.60, p=0.01), and frontal white (r=0.43, p=0.08) and gray matter (r=0.55, p=0.02). After excluding the three participants with Alzheimer's Disease, one per group, which is known to increase the relative proportion of "common deletion" in brain tissue, we found that a higher relative proportion of mtDNA with the "common deletion" was associated with worse neurocognitive impairment (r=0.99, p=0.003) only in the parietal white matter of HIV-infected individuals not using METH. Interestingly, in the parietal white matter of HIV-infected METH users, a higher relative proportion of "common deletion" was associated with higher CD4 counts, and inversely with degree of impairment (r=-0.86, p=0.06).

Conclusions: While an increased proportion of mtDNA carrying the "common deletion" was associated with increasing neurocognitive impairment in HIV-infected individuals as expected, METH use appeared to provide a protective effect. METH has been shown to increase autophagy and be neuroprotective at low doses. Further work is required to explore the role of mitochondrial injury in HIV-infected individuals and the effects of METH use on this damage.

500 Efavirenz-Induced Nitric Oxide Affects Mitochondrial Function in Glial Cells

Haryes A. Funes[1]; Fernando Alegre[2]; Miriam Polo[2]; Ana Blas-García[2]; **Juan V. Espluges**[3]; Nadezda Apostolova[4]
[1]*Universidad de Valencia, Valencia, Spain;* [2]*Universidad de Valencia/FISABIO, Valencia, Spain;* [3]*Universidad de Valencia/FISABIO/CIBERehd, Valencia, Spain;* [4]*Universidad Jaume I, Castellón, Spain*

Background: Neurological pathogenesis is closely associated with mitochondria. Nitric oxide (NO) is a ubiquitous central nervous system (CNS) mediator implicated in both mitochondrial dysfunction and inflammation. More than 50% of Efavirenz (EFV)-treated patients exhibit CNS-related effects that often require discontinuation of the therapy; moreover this drug has been recently linked to the development of HIV-associated neurological disorder (HAND). The underlying mechanisms of these effects are unknown however, recent evidence points to mitochondrial dysfunction. We analysed the ability of EFV to regulate NO generation in neurons and glial cells and the involvement of NO in the mitochondrial action of this anti-HIV.

Methods: Human cell lines glioma (U-251MG) and neuroblastoma (SH-SY5Y) and primary cultures of rat cortical neurons and astrocytes were exposed to short-term treatment with clinically relevant concentrations of EFV.

Results: EFV up-regulated inducible nitric oxide synthase (iNOS), thus enhancing NO production in glial cells whereas no up-regulation of NOS was observed in neurons. Incremented NO levels in glial cells had a bearing on mitochondrial function, as decreased overall O_2 consumption and increased mitochondrial superoxide generation induced by EFV were partially restored when NOS activation was pharmacologically inhibited. Analysis of the activity of the mitochondrial electron transport chain complexes revealed a major inhibitory effect of this drug on CI in both glial cells and neurons (1 and 6h), while other complexes were also affected (CIII and CIV) in glial cells (6 and 24h respectively). NO is capable of inhibiting and/or irreversibly damaging CIV, this possibility was endorsed by the fact that the decrease in CIV activity was reversed when a NOS inhibitor was added. Moreover, NO seems to be relevant to the bioenergetics effect of EFV observed in glial cells, as it was involved in the up-regulation of glycolysis that followed the mitochondrial interference induced by the drug.

Conclusions: EFV induces the synthesis of NO in glial cells which interferes with mitochondrial function in these cells, an effect not observed in neurons. These findings shed light on the mechanisms of the CNS side-effects of this drug, including the neuropsychiatric symptoms that appear soon after initiation of EFV therapy, which are sometimes accompanied by neuroinflammation, and long-term effects such as HAND.

THURSDAY, FEBRUARY 26, 2015

Session P-G9 Poster Session **Poster Hall**
2:30 pm – 4:00 pm

Neuropathogenesis Mechanisms

501 Role of HIV Strain, Accessory Proteins, and Cytokines in Macrophage HO-1 Deficiency

Alexander J. Gill; Patricia J. Vance; Ronald G. Collman; Dennis L. Kolson
University of Pennsylvania, Philadelphia, PA, US

Background: Protein expression of the cytoprotective enzyme heme oxygenase-1 (HO-1) is reduced in the prefrontal cortex of HIV+ individuals and negatively correlates with CNS viral replication and neuroinflammation. HIV infection of monocyte-derived macrophages (MDM) reduces HO-1 protein expression and pharmacologic rescue of HO-1 expression ameliorates HIV-MDM neurotoxin production. We now present data describing the change in HO-1 expression and neurotoxicity in MDM infected with 13 distinct HIV strains and the role of HIV accessory proteins and cytokine signaling in HIV-mediated HO-1 loss.

Methods: Using 13 macrophage-tropic HIV-1 strains, we infected MDM and determined the association between supernatant viral replication, glutamate, and neurotoxicity and HO-1 protein expression as measured by reverse transcriptase (RT) activity, enzymatic assay, neuron-based MAP2 ELISA, and Western blot analysis, respectively, on day 12 post-infection. Data was analyzed by ANOVA with Holm-Sidak post-test or Pearson's correlation.

Results: Most HIV replication variability in MDM was accounted for by viral strain (75.3%, $p<0.001$), although a significant, but smaller, proportion of variability was attributed to the donor (9.49%, $p<0.001$; $n=5$). Among the 13 viral strains, 11 significantly reduced MDM HO-1, but not HO-2, protein expression ($p<0.05$). This reduced HO-1 protein expression correlated significantly with increased viral replication, supernatant neurotoxicity, and extracellular glutamate ($p<0.001$). The viral inoculum of a single viral strain (89.6) predictably correlated positively with viral replication and supernatant neurotoxicity and negatively with HO-1 protein expression. Despite altered replication kinetics, infection of MDM with mutant 89.6 HIV molecular clones lacking Nef, Vpr, or Vpu, nonetheless reduced HO-1 protein expression ($p<0.05$). Chronic exposure (9 days) to the cytokines TNFα, IL-1β, IL-18, IL-23, and GM-CSF also reduced HO-1 protein expression in uninfected MDM ($p<0.05$).

Conclusions: Infection with most, if not all, macrophage-tropic HIV-1 strains reduce HO-1 protein expression in human macrophages. This reduction of HO-1 protein expression correlates with viral replication and likely augments HIV-MDM neurotoxin production. The HIV accessory proteins Nef, Vpr, and Vpu are not required for HIV-mediated HO-1 deficiency in macrophages. However, chronic inflammatory signaling associated with HIV replication may play a role in HIV-mediated reduction of HO-1.

502 Atorvastatin Reverses the HIV-induced HO-1 Defect in Primary Human Macrophages

Melanie R. Duncan; Alexander J. Gill; Anjana Yadav; Dennis L. Kolson; Ronald G. Collman
University of Pennsylvania, Philadelphia, PA, US

Background: HIV-associated neurocognitive disorders (HAND) are a collection of neurological deficits characterized by cognitive, motor, and behavior abnormalities, and remains a significant problem in ART-treated infected individuals. Neurological injury in HAND is a consequence of both persistent immune activation and the release of neurotoxins, such as glutamate, by HIV-infected and/or activated macrophages and microglia. Previous studies have implicated several macrophage enzymes in these neurodegenerative processes, including the cytoprotective enzyme heme oxygenase-1 (HO-1), glutaminase isoforms, and indoleamine 2,3-dioxygenase (IDO), that are disturbed by HIV infection. Statins (HMG-CoA reductase inhibitors) have pleiotropic immunomodulatory effects independent from their cholesterol-lowering abilities, such as downregulating monocyte/macrophage activation and inflammation. Therefore, we hypothesized that statins would modulate the levels of proteins associated with inflammation and neurological injury in HIV-1 infected macrophages.

Methods: Primary monocyte-derived macrophages (MDM) were infected *in vitro* with the macrophage-tropic HIV-1 strain YU-2. After 4-8 days, following establishment of infection (verified by supernatant p24 Gag antigen), cells were treated with atorvastatin (10 μM). After 6-48 hours, cells were lysed and protein expression of HO-1, IDO, and glutaminase isoforms were assessed by Western blot analysis.

Results: HIV-1 infection of MDM reduced HO-1 and increased IDO protein expression, as previously reported. We found that treatment with atorvastatin for 12-24 hours on day 8 post-infection increased HO-1 protein expression, partially reversing the HIV-mediated reduction. Similarly, treatment with atorvastatin for 6 hours on day 4 post-infection increased the level of HO-1. In contrast, atorvastatin had no effect on two isoforms of glutaminase, KGA and GAC. Effects on IDO were modest and inconsistent.

Conclusions: Atorvastatin partially reverses the HIV-mediated reduction of HO-1 in macrophages. Brain and macrophage HO-1 deficiency in HIV-infection has been implicated in HAND pathogenesis. Thus, statin drugs through HO-1 induction could be useful as an adjunctive therapy for HAND in HIV-infected ART-treated individuals.

503 Enhanced Antagonism of BST-2 by Neurovirulent SIV Envelope

Kenta Matsuda; Chia-Yen Chen; Fan Wu; Ronald Plishka; Alicia Buckler-White; Klaus Strebel; Vanessa M. Hirsch
National Institutes of Health (NIH), Bethesda, MD, US

Background: Although neuroAIDS or AIDS dementia caused by HIV-1 has been declining in clinical practice due to the use of Highly Active Antiretroviral Therapy (HAART), a milder neurologic disorder termed Minor Cognitive Motor Disorder (MCMD) continues to be a significant clinical problem. To develop new strategies to intervene in HIV disease progression in the brain, our lab has been developing a novel nonhuman primate neuroAIDS model by in vivo passage of SIVsmE543-3, a strain that is capable of inducing AIDS in the infected rhesus macaques but not SIV encephalitis (SIVE). As a result, we have recently isolated a viral strain, SIVsm804E, which can cause neuroAIDS in infected animals at high frequencies (Matsuda et al., JVI 2013, Matsuda et al., JVI 2014). A molecular clone, SIVsm804E CL757 was then isolated from the SIVsm804E viral swarm. Introduction of the gp41 cytoplasmic tail of Env of this molecular clone into the parental SIVsmE543-3 backbone, resulted in improvement of viral replication in monocyte derived macrophages (MDMs) in vitro. It has been previously reported that the cytoplasmic tail of gp41 of SIV plays an important role in the antagonism of the host factor, bone marrow stromal antigen 2 (BST-2, also known as Tetherin), that impairs the release of nascent viral particles from the virus-producing cells (Serra-Moreno et al., Cell host microbes 2011).

Methods: To determine whether efficient antagonism of BST-2 is responsible for the improvement of replication in macrophages, pulse-chase and immmunoprecipitation assays were conducted to compare the efficacy of BST-2 antagonism by the original SIVsmE543 to that of a variant with the cytoplasmic tail mutations found in SIVsm804E CL757.

Results: Preliminary data show that multiple mutations in the cytoplasmic tail of gp41 individually enhance viral release from the cells expressing BST-2. Since macrophages are the main target for viral infection and replication in the brain of SIV infected animals, our results suggest that our virus acquired mutations in the cytoplasmic tail of gp41 for efficient replication in the central nervous system (CNS).

Conclusions: Although SIV and HIV-1 utilize different viral proteins to antagonize BST-2, our data suggest that BST-2 may play an important role in the suppression of viral replication in the CNS and intervention of viral factors that antagonize BST-2 could be a novel strategy for prevention of disease progression in the CNS during HAART.

504 MEMRI Reflects HIV-1-Associated Human Pathobiology in a Rodent NeuroAIDS Model

Aditya N. Bade; Santhi Gorantla; Prasanta K. Dash; Edward Makarov; Balasrinivasa R. Sajja; Larisa Poluektova; Howard Gendelman; Michael Boska; Yutong Liu
University of Nebraska Medical Center, Omaha, NE, US

Background: Progressive human immunodeficiency viral (HIV) infection commonly leads to a constellation of cognitive, motor and behavioral impairments. While antiretroviral therapy (ART) reduces disease severity, it does not affect disease prevalence. There are no diagnostic biomarkers for neuroAIDS and co-morbid conditions must first be excluded. To this end, we applied manganese (Mn^{2+})-enhanced magnetic resonance imaging (MEMRI) to noninvasively assess virus-induced neuropathology in a human disease relevant rodent neuroAIDS model.

Methods: Humanized mice (NOD/scid-IL-2Rγc^{null}) reconstituted at birth with human CD34+ hematopoietic stem cells were infected with HIV-1_{ADA} (i.p. at 10^4 $TCID_{50}$) at 22 weeks of age. Infection was followed for 16 weeks. Uninfected humanized mice used as controls. Flow cytometry for peripheral blood leukocytes was performed at 2, 4, 7, 10, 13 and 16 weeks post infection (WPI) to determine proportions of peripheral human immune cells. Plasma viral RNA copies/ml (viral load, VL) measures were performed at 2, 7, 16 WPI. Animals were MEMRI tested at 16 wpi to measure signal enhancement and morphological changes. Furthermore, an MEMRI-based brain atlas, the T_1-wt signal enhancement on 41-brain regions/sub-regions was calculated and student's t-test performed to examine enhancement significance. Immunohistochemistry was performed at study termination. Brain sections were stained for human cells, virus infected human cells, neuronal, oligodendrocytes and glial inflammatory markers.

Results: CD4+ T cell decline and concomitant increases in CD8+ T cells were seen in the HIV-1 infected mice. Control uninfected animals showed no changes in cell numbers. VL values peaked at the 2nd week after HIV-1 infection and were sustained throughout the study. Human (HLA-DR+) cells infiltrated the brains of infected and control mice were

seen predominantly in meninges and perivascular spaces. Few HIV-1p24+ human cells were observed. Altered MEMRI signal enhancement was readily observed in affected brain regions of infected animals. These included, but were not limited to, the hippocampus, amygdala, thalamus and cerebellum. MEMRI findings paralleled levels of infection, neuroinflammation and neuronal injury. These proved to be an accurate measure of virus-induced neuropathology.

Conclusions: These MEMRI signal enhancements demonstrates the complexities of HIV-1 associated neuropathology in rodents that reflect, in measure, the clinical manifestations of neuroAIDS as it is seen in a human host.

505 Detectable CSF Tat Despite Dual Compartment HIV Viral Suppression With cART

Bruce Brew[1]; Lucette A. Cysique[2]; Simon Jones[4]; Tory Johnson[3]; Avindra Nath[3]

[1]St Vincent's Hospital, Sydney, Sydney, Australia; [2]Neuroscience Research Australia, Sydney, Australia; [3]National Institute of Neurological Disorders and Stroke, Bethesda, MD, US; [4]St Vincent's Centre for Applied Medical Research, Sydney, Australia

Background: HIV associated neurocognitive disorders (HAND) persist despite HIV suppression in both the blood and cerebrospinal fluid (CSF). Antiretroviral drugs do not prevent post integration transcription of viral components such as tat. Further, tat is known to be neurotoxic and able to exit the infected cell. We therefore hypothesized that the presence of HAND in the context of HIV suppression in both blood and CSF would be related to the presence of tat in the CSF. We further hypothesized that the putative HIV latency biomarker BCL11b would be elevated in those samples where tat was not detectable.

Methods: Thirty seven CSF samples from 37 HIV+ adults (1 female) with viral suppression in both blood and CSF (<20 cpml) were assessed for the presence and amount of tat by an ELISA assay. All the patients had been assessed medically and neuropsychologically (NP) as part of an HIV and aging prospective study whose inclusion criteria were: aged 45+, CD4 nadir≤350; HIV duration ≥5 years, ≥6 months cART, and exclusion were lifetime neurological and psychiatric disorders including alcohol/substance use disorder within 12 months of study entry. Using standard criteria, NP-HAND was present in 65% (Asymptomatic Neurocognitive Impairment (ANI) in 14; Mild Neurocognitive Disorder (MND) in 7; and HIV-associated dementia (HAD) in 3). CSF BCL11B was detected by immunoblot assay using anti-BCL11b antibody while levels were quantified by measuring the integrated intensity of fluorescence from the secondary conjugated antibody.

Results: CSF tat was found in five of the 37 samples (range: 27-375pg/ml). There was no correlation with HAND: 3 of the 5 were NP-normal, 1 had ANI and the other had HAD. BCL11b integrated intensity levels were 0.24 ± 0.04 (mean ± sem). There was no correlation between CSF tat and BCL11b.

Conclusions: CSF tat is detectable in 13.5% of dual compartment virally suppressed patients. The lack of correlation with HAND may be related to intermittent tat production, tat polymerization rendering the current assay insensitive, or other causal factors for HAND (other transcripts such as vpr,nef or drug toxicity, inactive HAND). Nonetheless, the presence of tat despite viral suppression has implications for eradication strategies especially those that involve cART.

506 DNA Methylation Changes in HIV-Positive Men With Cognitive Decline

Jeremy Martinson; Gregory Joseph; Lawrence Kingsley; James T. Becker
Pitt Mens Study

University of Pittsburgh, Pittsburgh, PA, US

Background: A subset of aging individuals with chronic, treated, HIV infection develop neurocognitive decline. Epigenetic factors, such as DNA methylation, have been implicated in the aging process and the development of chronic diseases. We hypothesize that long-term treated HIV infection has had a detectable impact on DNA methylation in these individuals, and this epigenetic change is associated with their cognitive impairment.

Methods: Within the Pitt Mens Study, we identified 8 men with cognitive decline (3 seropositive and 5 seronegative), and matched them with 8 seropositive controls (matched on age and length of time seropositive) and 8 seronegative controls (matched on age). For each of these 24 men we obtained a PBMC pellet from a recent clinic visit and an archival PBMC collected on average ten years earlier. The DNA methylation profile was then determined for each time point using the Illumina HumanMethylation450K microarray, and the change in methylation status at each of the 480,000 CpG sites present on the microarray was calculated.

Results: Over the ten-year time period, DNA methylation levels changed little in any of the seropositive and seronegative control samples. In stark contrast, DNA methylation was drastically perturbed in every seropositive and seronegative sample with cognitive decline. The CpG sites affected are different in each individual: no consistent Methylation Variable Positions (MVPs) or Differentially Methylated Regions (DMRs) were found by bioinformatic analysis, and pairwise comparisons showed that the magnitude and direction of the methylation change at each site varied greatly between individuals. The perturbations were similar in both seropositive and seronegative samples, but the average age of onset of cognitive decline was 10.5 years younger in the seropositive samples.

Conclusions: We determined that the development of cognitive decline in our samples is accompanied by a chaotic change in DNA methylation. This may be due to changes in the populations of cells that make up the PBMC samples obtained for each person, but it is more likely that this "methylation entropy" reflects random changes in DNA methylation in the genome of affected individuals. It is not clear what initial events trigger this chaotic change, nor is it clear how this increase in entropy affects cognition, but we suggest that DNA methylation may be a biomarker of risk for cognitive decline, and should also be investigated in other diseases of aging in HIV-positive individuals.

507 HIV Induces Astrocyte Senescence and Is Reversed by Beta-Catenin Induction

Chunjiang Yu; **Victoria Lutgen**; Lena Al-Harthi

Rush University Medical Center, Chicago, IL, US

Background: Neuroinflammation and neurodegeneration are hallmarks of HIV-Associated Neurocognitive Disorders (HAND). Astrocyte senescence induces neuropathologies due to increased oxidative stress and altered cytokine secretion leading to neuroinflammation. These processes reduce the neuroprotective capacity of astrocytes leading to long-term inflammation and neurodegeneration. We evaluated the impact of HIV on astrocyte senescence and explored the role of Wnt/b-catenin, a pro-survival pathway, in astrocyte senescence in the context of HIV.

Methods: Human Fetal Astrocytes (HFAs) were infected with VSVG pseudotyped-HIV_{BAL} or transfected with a full length HIV_{BAL} plasmid ($pHIV_{BAL}$) or corresponding controls. HFAs were transfected with β-catenin siRNA, scrambled siRNA, constitutively active β-catenin plasmid (pABC), or background. Dickkopf-related protein 1 (DKK1) was used as an antagonist of the Wnt/β-catenin pathway. Six days post treatment, HFAs were fixed and stained for senescence-associated β-galactosidase (SA-β-gal); percent positive SA-β-gal cells were recorded.

Results: VSVG-HIV_{BAL} and $pHIV_{BAL}$ significantly induced SA-β-gal staining in HFAs by 5- and 2-folds, respectively. β-catenin knockdown or antagonizing Wnt/b-catenin signaling through DKK-1 treatment induced SA-b-gal expression in HFA by ≥3.5 folds. Conversely, pABC inhibited HFA senescence by ≈60%.

Conclusions: HIV induces astrocyte senescence. Given that we previously demonstrated that HIV diminishes b-catenin signaling in astrocytes and we show here that reduction in b-catenin expression promotes while induction of b-catenin protects against astrocyte senescence suggests that HIV induces astrocyte senescence through inhibition of b-catenin

signaling. If so, activation of Wnt/b-catenin in astrocytes may emerge as a prominent pathway to reverse astrocyte senescence associated with aging and/or neurodegenerative diseases beyond HAND.

508 Wnts-Mediated Astrocyte/CD8+ T-Cell Interactions Impacting HIV Neuropathogenesis

Maureen H. Richards[1]; Melanie S. Seaton[1]; Stephanie Kim[2]; Srinivasa Narasipura[1]; Lena Al-Harthi[1]

[1]Rush University Medical Center, Chicago, IL, US; [2]Brown University, Boston, MA, US

Background: Depletion of CD8+ T cells accelerates neuroAIDS, although there is no clear evidence that CD8+ T cells control HIV/SIV in the CNS. A subset of CD8+ T cells, $CD4^{dim}CD8^{bright}$ T cells (DP T cells), is enriched in anti-HIV responses. This phenotype is generated through induction of Wnt/b-catenin signaling in CD8+ T cells. Wnts, small secreted glycoproteins, initiate Wnt/b-catenin signaling leading to gene regulation. Given that astrocytes are a rich source of Wnts, we evaluated whether astrocytes drive DP expression in vitro and in vivo.

Methods: Wnts mRNA and protein from human progenitor-derived astrocytes (PDAs) were determined by qRT-PCR and western blot, respectively. Day three-Astrocyte Conditioned Media (ACM) was added to αCD3/CD28 activated PBMCs and percentage of DP T cells was assessed at day six by flow. Wnts were depleted from ACMs by protein A/G magnetic beads coated with anti-Wnt 1, Wnt2b, Wnt 3, Wnt 5b, Wnt 10b, or IgG1 isotype control. NOD/SCID/IL-2rcγ -/- (NSG) mice were reconstituted with $2x10^7$ PBMCs (NSG-HuPBMCs) and infected by intraperitoneal injection with 10^4 $TCID_{50}$ HIV_{BAL} at week 1. Three weeks post-infection, brain lymphocytes were isolated and expression of CD8, CD4, and HIVp24 determined by flow. Lastly, violet-labeled CD8+ T cells were injected into NSG brain, re-isolated at 1 week, and evaluated for CD4, CD45RA, CD27, CD28, and CCR7 expression by flow.

Results: PDAs secrete Wnts 1, 2b, 3, 5b, and 10b. ACM induced DP expression by 2-fold in a Wnt-dependent manner. CD8 Single Positive (SP) and DP T cells are found in the brain of HIV+ NSG-HuPBMCs mice. DP cells harbor HIV, but interestingly, at three weeks post-infection, greater than 90% of CD4 SP T cells were depleted, while 25% of DP cells survived. Brain injection of Violet-labeled CD8+ T cells induced DP expression by 10-fold, where >80% of DP and CD8 SP T cells expressed surface markers indicative of a Terminal Effector Memory (TEMRA) phenotype ($CCR7^-CD27^-CD28^-CD45RA^+$).

Conclusions: Astrocytes drive DP expression through Wnts. DP T cells are present in the CNS, are TEMRA, and HIV infected. Unlike CD4 SP T cells, DP T cells survive longer and may constitute a novel HIV CNS reservoir. These studies highlight a dynamic interaction between astrocytes and CD8 T cells, which can skew their differentiation and lead to a phenotype that, on one hand, can control HIV in the CNS but, on the other, heightens inflammatory responses in the CNS, contributing to HAND pathology.

TUESDAY, FEBRUARY 24, 2015

Session P-H1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Pharmacokinetics, Pharmacodynamics, and Adherence

509 HIV-1 Attachment Inhibitor Prodrug BMS-663068: Model-Based Dose Selection

Ishani Savant Landry[1]; Li Zhu[1]; Malaz Abutarif[1]; Matthew Hruska[1]; Brian M. Sadler[2]; Maria Pitsiu[3]; George J. Hanna[1]; David W. Boulton[1]; Richard Bertz[1]

[1]Bristol-Myers Squibb, Princeton, NJ, US; [2]ICON plc, Cary, NC, US; [3]ICON plc, Manchester, United Kingdom

Background: BMS-663068 is a prodrug of BMS-626529, an attachment inhibitor that binds to HIV-1 gp120, preventing initial viral attachment and entry into host CD4+ T-cells. Pharmacokinetic (PK)/pharmacodynamic (PD) modeling of Phase 2 data was performed to guide dose selection for subsequent studies.

Methods: PK/PD data from two Phase 2 studies (AI438006, AI438011) in HIV-1-infected subjects (N=244) were used to develop a population PK model for BMS-626529 using non-linear mixed effects modelling (NONMEM v.7.2.0). Subsequently, relationships between IC_{50}-normalized BMS-626529 systemic exposure (C_{max}, C_{ssavg}, C_{tau}) and efficacy/safety variables during monotherapy or after 24/48 weeks of combination therapy, were investigated using linear models. Monte-Carlo methods were used to assess the probability of achieving a decline of >0.5 (per FDA draft guidance) or >1.0 $\log_{10}$ c/mL in HIV-1 RNA from baseline (BL) as a function of BMS-626529 systemic exposure after 7 days of BMS-663068 monotherapy for 5 proposed BMS-663068 doses (400mg/600mg [not studied clinically]/800mg BID and 600mg/1200mg QD).

Results: A 2-compartment model with 1st-order elimination from the central compartment, zero-order release into a hypothetical absorption compartment, and 1st-order absorption into the central compartment described the PK of BMS-626529. The categorical covariates (ritonavir co-administration, BMS-663068 formulation type) and the continuous covariates (lean body mass, BL CD8%) were significant in the model. After 7 days of BMS-663068 monotherapy, BL BMS-626529 protein-binding adjusted IC_{50} ($PBAIC_{50}$) influenced HIV-1 RNA decline and a clear relationship was observed between $\log_e$-transformed $PBAIC_{50}$-adjusted C_{tau} and change in HIV-1 RNA from BL ($\log_{10}$ c/mL). No trends were observed between BMS-626529 systemic exposure and other efficacy/safety variables during BMS-663068 monotherapy or after 24/48 weeks of combination therapy. After 7 days of simulated BMS-663068 monotherapy, the probability of achieving a decline in HIV-1 RNA of >0.5 $\log_{10}$ c/mL or >1 $\log_{10}$ c/mL as a function of $\log_e$ $PBAIC_{50}$-adjusted C_{tau} was predicted to be 99–100% and 57–73%, respectively across the doses (Table).

Simulated BMS-663068 dose	Probability of achieving a decline in HIV-1 RNA of >0.5 $\log_{10}$ c/mL as a function of $\log_e$ $PBAIC_{50}$-adjusted C_{tau}, %	Probability of achieving a decline in HIV-1 RNA of >1.0 $\log_{10}$ c/mL as a function of $\log_e$ $PBAIC_{50}$-adjusted C_{tau}, %
400 mg BID	100.0	68.0
600 mg BID (not studied clinically)	100.0	71.1
800 mg BID	99.9	72.6
600 mg QD	99.5	57.4
1200 mg QD	99.8	60.8

Predicted probability of achieving a decline in HIV-1 RNA of >0.5 or >1.0 $\log_{10}$ copies/mL after 7 days of BMS-663068 monotherapy, as a function of $\log_e$ $PBAIC_{50}$-adjusted C_{tau}

Conclusions: Simulations showed an advantage of BID over QD dosing and a similar probability of achieving a decline of >1 $\log_{10}$ c/mL across the 400, 600 and 800mg BID doses. Combined with clinical and safety observations, a 600mg BID dose of BMS-663068 was predicted to have the best benefit–risk profile and was selected for further study.

510 Pharmacokinetic and Pharmacodynamic Evaluation of NNRTI IQP-0528 DuoGel™ in Macaques

Lara E. Pereira[1]; Pedro Mesquita[2]; **Anthony Ham**[3]; Tyana Singletary[4]; Janet McNicholl[5]; Karen W. Buckheit[3]; Robert Buckheit[3]; James M. Smith[5]

[1]LifeSource Biomedical LLC,, Moffett Field, CA, US; [2]Albert Einstein College of Medicine, Bronx, NY, US; [3]ImQuest BioSciences,, Frederick, MD, US; [4]Anyar Inc., Fort Walton Beach, FL, US; [5]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: Unprotected receptive anal intercourse (RAI) is also practiced by women, providing strong rationale for the development of an HIV microbicide gel that is suitable for both rectal and vaginal applications. This would remove the need for separate products and dosages for women who engage in RAI and vaginal intercourse, thereby helping to increase user adherence and potentially cutting costs associated with separate products. A DuoGel™ product containing 1% wt/vol IQP-0528, which has non-nucleoside reverse transcriptase and entry inhibitory activities, was developed and first evaluated vaginally in pigtailed (PM) and rhesus (RM) macaques.

Methods: DuoGel™ formulation was optimized for dual compartment application. A 1.5 ml volume of 1% IQP-0528 DuoGel™ was applied vaginally to 6 SHIV+ female RM and 6 naïve female PM. Blood, vaginal pH measurements, cervicovaginal lavage, and vaginal and rectal spears were collected before, and up to 24 hours after gel application. Vaginal and rectal biopsies were also collected from PM at 24 hours. The RM were euthanized at 4 hours, and vaginal, cervical, rectal, and regional lymph node tissues were harvested for drug analysis. Anti-viral activity was tested *ex vivo* by co-culturing RM vaginal tissues with activated human peripheral blood mononuclear cells (PBMC), and measuring p24 levels up to 10 days after challenge with HIV-1_{Ba-L}. Drug levels in plasma, vaginal fluids, and tissues were determined using LC-MS.

Results: In RM, median levels of IQP-0528 were between 10^4-10^5 ng/g in vaginal and cervical tissue, and 10^5-10^7 ng/ml in vaginal fluids for 4 hours after gel application. Bi-directional dosing was shown by median IQP-0528 levels being between 10^3-10^4 ng/g in rectal tissues. Similar levels were observed in PM vaginal fluids for 4 hours post gel application, but IQP-0528 was not detected in the rectum. Vaginal pH remained within normal range for both species (6.5-9). Vaginal tissues obtained from RM at necropsy protected co-cultured PBMC from HIV-1 infection *ex vivo*, with a viral inhibition range of 90-100%. Anti-viral activity was observed in vaginal tissues that were proximal, medial, and distal relative to the cervix. Viral inhibition was not detected in baseline tissue samples.

Conclusions: These data suggest that 1.5 ml of DuoGel™ delivers IQP-0528 throughout the macaque vaginal compartment at levels that are highly inhibitory to HIV-1 infection. Rectal PK studies are underway.

511 Tenofovir PK in Adults With Renal Dysfunction on LPV/r and NNRTI-Based ART

Tim R. Cressey[1]; Anchalee Avihingsanon[2]; Guttiga Halue[3]; Prattana Leenasirimakul[4]; Pra-ornsuda Sukrakanchana[5]; Anthony T. Podany[6]; Courtney Fletcher[6]; Gonzague Jourdain[5]; Virat Klinbuayaem[7]; Chureeratana Bowonwatanuwong[8]

[1]PHPT-IRD UMI 174 Chiang Mai University/Harvard School of Public Health, Chiang Mai, Thailand; [2]HIV Netherlands Australia Thailand Research Collaboration, Bangkok, Thailand; [3]Phayao Hospital, Phayao, Thailand; [4]Nakornping Hospital, Chiang Mai, Thailand; [5]Chiang Mai University, Chiang Mai, Thailand; [6]University of Nebraska Medical Center, Omaha, NE, US; [7]Sanpatong Hospital, Sanpatong, Thailand; [8]Chonburi Hospital, Chonburi, Thailand

Background: The recommended tenofovir disoproxil fumarate (TDF) dose is 300 mg every 48 hours for adults with moderate renal function impairment (creatinine clearance 30-49 mL/min). Coadminsitration of TDF with lopinavir/ritonavir (LPV/r) increases plasma tenofovir (TFV) concentrations in adults with normal renal function. We compared the plasma and intracellular pharmacokinetics (PK) of TDF 300 mg every 48 hours in HIV-infected adults with moderate renal function impairment receiving LPV/r and NNRTI-based antiretroviral therapy.

Methods: Data were collected within a phase I, non-randomized, open-label pharmacokinetic study of TDF in patients with renal dysfunction (ClinicalTrials.gov Identifier: NCT01671982). Consenting HIV-positive adults with a confirmed creatinine clearance (CrCL) 30 to <50 mL/min receiving TDF 300 mg every 48 hours per standard of care as part of a LPV/r- or NNRTI-based ART and an HIV-1 RNA viral load (VL) <50 copies/mL were included. HBs-antigen positive adults were excluded. Intensive steady-state 48-hour blood sampling for PK assessment was performed, blood samples were collected pre-dose and then at 0.5, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 12, 24, 36, 48 hours post-dose. Peripheral blood mononuclear cells (PBMCs) were also collected at 48 hours post-dose for assessment on intracellular tenofovir di-phosphate concentrations. PK parameters were calculated using non-compartmental analysis.

Results: 40 HIV-infected adults (55% female) were enrolled. Median (range) age was 56 years (39-82), weight 51 kg (38-80), serum creatinine (SCr) 1.3 mg/dL (0.8-2.1), CrCL 43.9 mL/min (30.9-49.7) and CD4 count 502 cells/mm^3 (113-1063). Tenofovir PK data were evaluable from 19 subjects receiving an NNRTI- (9 nevirapine and 10 efavirenz) and 18 receiving LPV/r-based HAART. Tenofovir plasma and intracellular PK parameters are presented in the table below:

Mean tenofovir plasma AUC_{0-24} was 1.7-fold higher with coadminsitration of LPV/r compared to NNRTIs.

PK Parameters	TDF 300 mg every 48 hours NNRTI-based HAART (n=19)	TDF 300 mg every 48 hours LPV/r-based HAART (n=18)	P-Value*
TFV Plasma			
AUC_{0-48} (mg.hr/L)	5.76 (3.34 - 11.08)	9.61 (6.06 - 18.92)	<0.001
Cmax (mg/L)	0.44 (0.23 - 0.67)	0.68 (0.44 - 1.31)	<0.001
Clast (mg/L)	0.04 (0.02 - 0.10)	0.07 (0.03 - 0.11)	0.004
CL/F (L/hr)	23.60 (12.26 - 40.73)	14.15 (7.19 - 22.44)	<0.001
TFV-DP Intracellular			
Clast (fmol/10^6 cells)	130 (27-945)	188 (25-497)	0.504

Values: median (range). *signed rank test.

Tenofovir PK Parameters

Conclusions: Tenofovir plasma exposure was significantly higher with LPV/r versus NNRTI based ART in patients with moderate renal function impairment. In contrast, trough intracellular TFV-diphosphate concentrations were similar between the two ART regimens.

512 Population Pharmacokinetics of Cotrimoxazole West African HIV-Infected Children

Claire Pressiat[1]; Sihem Benaboud[2]; Jean-Marc Treluyer[1]; Véronique Méa-Assande[3]; Caroline Yonaba[4]; Sophie Dattez[5]; Diarra Ye[6]; Yi ZHENG[1]; **Valeriane Leroy**[5]; Déborah HIRT[1]
MONOD ANRS 12206

[1]Paris Descartes University, EA 08, Paris, France; [2]Clinical Pharmacology Department, AP-HP, Paris Centre Hospital Group, Paris, France; [3]Avocatier Health Center, Abidjan, Côte d'Ivoire; [4]Department of Paediatrics, CHU Yalgado Ouedraogo, Ouagadougou, Burkina Faso; [5]Institute of Public Health, Epidemiology and Development (ISPED), University of Bordeaux, Bordeaux, France; [6]Department of Paediatrics, CHU Charles de Gaulle, Université de Ouagadougou, Ouagadougou, Burkina Faso

Background: Cotrimoxazole (association of sulfamethoxazole (SMX) and trimethoprim (TMP)) is recommended to prevent opportunistic infections in HIV-infected children. Despite the overwhelming use of this medication, few pharmacokinetics (PK) data are available in children. We investigated the PK of cotrimoxazole in a therapeutic cohort of children initiated < 2 years of age on a combination antiretroviral therapy (cART).

Methods: All HIV-infected children diagnosed before 2 years of age, and confirmed by DNA-PCR were enrolled in an initial therapeutic cohort offering a cART with cotrimoxazole prophylaxis (TMP/SMX: 200/40/day once daily) in Ouagadougou (Burkina Faso), and Abidjan (Ivory Coast). Quantification of TMP and SMX in human plasma collected 6 months after cART initiation was performed using a validated liquid chromatography method with UV detector. Plasma concentrations collected from HIV-infected children aged from 6 months to 2.5 years were analyzed using a nonlinear mixed effects modeling, with NONMEM software. Estimated individual PK parameters were used to calculate individual exposures (Area under curves : AUC) to TMP and SMX. Pharmacogenetic studies are underway.

Results: Overall, 114 children with a median age of 1.6 years, a median weight of 9 kg, and a sex ratio (M/F) of 0.88 were analysed. TMP's and SMX's PK were described by a one-compartment model with first-order absorption and elimination. A very large interindividual variability in cotrimoxazole concentrations was pointed out. With the dosing regimen currently recommended exposure are much lower in one third of the children than those found in adults. In order to maintain a comparable exposure as in adults in this population, an increase of the dose should be considered. In addition, a trend was observed between cotrimoxazole lower exposure and infection with malaria (p=0.08).

Conclusions: With the dosing regimen currently recommended one third of the children are underexposed compared to adults. Moreover, a trend to more malaria infection has been suggested in children with low SMX exposure.

513 ART Choice Impacts Antimalarial Exposure and Treatment Outcomes in Ugandan Children

Sunil Parikh[2]; Norah Mwebaza[3]; Richard Kajubi[3]; Joshua Ssebuliba[3]; Sylvia Kiconco[3]; Liusheng Huang[1]; Qin Gao[1]; Abel Kakuru[3]; Jane Achan[3]; **Francesca T. Aweeka**[1]

[1]University of California, San Francisco, San Francisco, CA, US; [2]Yale University, New Haven, CT, US; [3]Makerere University College of Health Sciences, Kampala, Uganda

Background: Treatment guidelines for HIV and malaria co-infected children are not developed despite concern that drug interactions impact malaria outcomes. Artemether-lumefantrine (AR-LR), contains long-acting LR with a predominant impact on reinfection rates. Previously, HIV infected children, managed with lopinavir/ritonavir (LPV/r)-based ART, had lower risk for malaria compared to those on efavirenz (EFV) or nevirapine (NVP)-based ART. The pharmacological basis for these distinctions has not been fully addressed.

Methods: Using intensive and population methods, we investigated the pharmacokinetics (PK) and pharmacodynamics (PD) of AR-LR as treatment, in the context of varying ART in HIV infected children 0.5 to 8yrs in the highly endemic region of Tororo. HIV-uninfected children served as *controls* (C). Intensive (area under the concentration-time curve, AUC) and sparse PK were done over 21d with clinical and parasitological response followed for 42 d. AR, active dihydroartemisinin (DHA), and LR were measured by LC tandem MS.

Results: 130 children had intensive PK (n=30LPV/r; 19EFV; 30NVP and 51C); 89 children had sparse PK (n=26LPV/r; 7EFV; 18NVP and 38C). Lower AR AUC was seen with EFV and NVP compared with C [GMR; EFV:0.41 (p=0.0003); NVP:0.36 (p<0.001)]; DHA was reduced only with EFV [GMR 0.29 (p<0.0001)]. Notably, LPV/r and EFV had dramatic and converse effects on LR AUC; LPV/r and EFV resulted in 2 fold *higher* and 3 fold *lower* AUC, respectively. Nearly all EFV children exhibited undetectable LR day 14 and 21 levels (Table). Cumulative 28d risk of parasitologic failure was 11, 44 and 32%, for children on LPV/r, EFV and NVP, respectively. Children on EFV vs. LPV/r had a 4.4 fold higher risk of parasitologic failure at 28d (p=0.007). Recurrent parasitemia risk at 28d was linked with LR AUC (p=0.03) and day 7 levels (HR 0.55, p=0.001). Day 7 <175 ng/mL, a key threshold for clinical outcomes, was linked with 2.5-fold higher risk of recurrent parasitemia (p=0.012) with 9, 89, and 10% of LPV/r, EFV and NVP children below this threshold.

Intensive PK (n=130)

	AR-LR alone (C)	AR-LR+LPV/r		AR-LR+EFV		AR-LR+NVP	
	GM; 95%CI (n=51)	GM; 95%CI (n=30)	GMR, LPV/C	GM; 95%CI (n=19)	GMR, EFV/C	GM; 95%CI (n=30)	GMR, NVP/C
$AR\_AUC_{0\text{-}8}$	122 (98.0-152)	97.1 (68.2-138)	0.80	50.0 (33.3-75.0)	0.41*	43.3 (31.7-59.0)	0.36**
$DHA\_AUC_{0\text{-}8}$	217 (174-271)	180 (132-246)	0.83	62.0 (40.6-94.8)	0.29**	148 (116-189)	0.68***
$LR\_AUC_{0\text{-}\infty}$	269 (236-306)	564 (423-752)	2.1**	101 (71.4-143)	0.38**	278 (218-355)	1.0

GM: geometric mean; CI: confidence interval, GMR: geometric mean ratio. AR and DHA $AUC_{0\text{-}8}$ unit is hr·ng/mL. $LR\_AUC_{0\text{-}\infty}$ unit is hr·µg/mL.

Intensive and population PK (n=219)

	AR-LR alone (C)	AR-LR+LPV/r		AR-LR+EFV		AR-LR+NVP	
	Median (IQR), n=89	Median (IQR), n=56	MR, LPV/C	Median (IQR), n=26	MR, EFV/C	Median (IQR), n=48	MR, NVP/C
LR C_{7d}	321 (246, 467)	1160 (497, 2150)	3.6**	92.6 (55.3, 126)	0.29**	412 (276, 660)	1.3***
LR C_{14d}	94.9 (64.2, 133)	314 (159, 570)	3.3**	BLQ (BLQ, BLQ)	<1**	115 (68.3, 179)	1.2***
LR C_{21d}	BLQ (BLQ, 63.4)	146 (81.2, 250)	>1**	BLQ (BLQ, BLQ)	<1*	BLQ (BLQ, 93.2)	

LR C7d, C14d, and C21d are LR concentrations (ng/mL) on days 7,14 and 21 respectively ; reported as median with IQR, interquartile range.

MR, median ratio. * P<0.0005, **p<0.0001, ***p<0.05

Conclusions: Based on PK for 219 malaria episodes, EFV-based ART results in clinically significant reductions in AR and LR exposure. LR exposure is strongly linked to parasitological failure and 89% of EFV children had day 7 LR <175 ng/mL. In the face of emerging resistance, optimum AR-LR dosing is critical. Low exposure to both AR and LR with EFV-based ART suggests need for improved dosing guidelines in children.

514 Exploring Long-Term Adherence Markers Using Hair and Dried Blood Spots in iPrEX OLE

Monica Gandhi[1]; David V. Glidden[1]; Albert Liu[2]; Peter L. Anderson[7]; Howard Horng[1]; Juan Guanira[3]; Beatriz Grinsztejn[4]; Suwat Chariyalertsak[5]; Linda-Gail Bekker[6]; Robert M. Grant[1]
iPrEX OLE

[1]University of California San Francisco, San Francisco, CA, US; [2]San Francisco Department of Public Health, San Francisco, CA, US; [3]Investigaciones Medicas en Salud, Lima, Peru; [4]Instituto de Pesquisa Clinica Evandro Chagas, Rio de Janeiro, Brazil; [5]Chiang Mai University, Chiang Mai, Thailand; [6]University of Cape Town, Cape Town, South Africa; [7]University of Colorado, Denver, CO, US

Background: Adherence to tenofovir/emtricitabine (TFV/FTC)-based PrEP is critical to efficacy. The limitations of self-reported adherence in reliably capturing TFV/FTC exposure are well-known, raising interest in pharmacologic measures where drug levels are assessed in a biomatrix (e.g. plasma, peripheral blood mononuclear cells (PBMCs), dried blood spots (DBS), hair). Plasma and PBMC collection can be challenging, require refrigeration and biohazard precautions, and represent short-term exposure. Hair and DBS collection provide feasibility advantages in resource-limited settings and levels in these matrices represent longer-term exposure, although correlation between these measures is unknown. We report for the first time the correlation of drug levels and concordance of drug detection in hair and DBS in PrEP.

Methods: The iPrEX Open Label Extension (OLE) enrolled 1603 HIV-negative MSM and transwomen who previously enrolled in PrEP trials, of which 1225 initiated PrEP. DBS were collected at 4 and 8 weeks following PrEP initiation and then every 12 weeks. Hair samples were collected on an opt-in basis every 12 weeks. Hair and DBS levels of drugs were measured via liquid chromatography/ tandem mass spectrometry. Spearman's correlation coefficients assessed relationships between TFV and FTC levels in hair and TFV-disphosphate (TFV-DP) and FTC-triphosphate (FTC-TP) concentrations in red blood cells measured with DBS.

Results: 806 paired hair-DBS samples were available for comparison in iPrEX OLE. TFV levels in hair and TFV-DP levels in DBS were strongly correlated (r 0.734, p <0.001), as were TFV in hair and FTC-TP in DBS (r 0.781, p<0.001) and FTC in hair and TFV-DP in DBS (r 0.742, p <0.001); FTC in hair and FTC-TP in DBS were more modestly correlated (r 0.587, p <0.001). A comparison of the levels of detection for the relevant antiretroviral or metabolite in the two matrices are shown in the Table. Concentrations of drugs in either matrix were mostly concordant in terms of detectability.

Concordance of PrEP drug detection in hair and DBS in 806 paired samples, iPrEx OLE				
Drug detection	Detectable in hair and DBS (%)	Detectable in hair, not DBS (%)	Detectable in DBS, not hair (%)	Undetectable in both matrices (%)
TFV in hair, TFV-DP in DBS	72%	3%	15%	10%
TFV in hair, FTC-TP in DBS	71%	5%	5%	19%
FTC in hair, FTC-TP in DBS	62%	14%	5%	19%
FTC in hair, TFV-DP in DBS	74%	2%	13%	11%

Conclusions: This is the first study to ever examine the correlation between concentrations of PrEP medications in hair samples and DBS, matrices in which long-term exposure to PrEP are captured. Strong correlations were observed between drug levels in hair and DBS. Further study is needed to compare the elimination kinetics and variability of TFV and FTC in hair versus TFV-DP and FTC-TP in DBS to guide the use of these measures for quantifying cumulative versus recent adherence in PrEP trials and real-world settings.

TUESDAY, FEBRUARY 24, 2015

Session P-H2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Pharmacogenomics

515 UGT1A1 Genotype Predicts Bilirubin-Related Discontinuation of Atazanavir/Ritonavir

Saran Vardhanabhuti[1]; Heather J. Ribaudo[1]; Raphael J. Landovitz[2]; Igho Ofotokun[3]; Jeffrey L. Lennox[3]; Judith S. Currier[2]; Lana M. Olson[4]; David W. Haas[4]

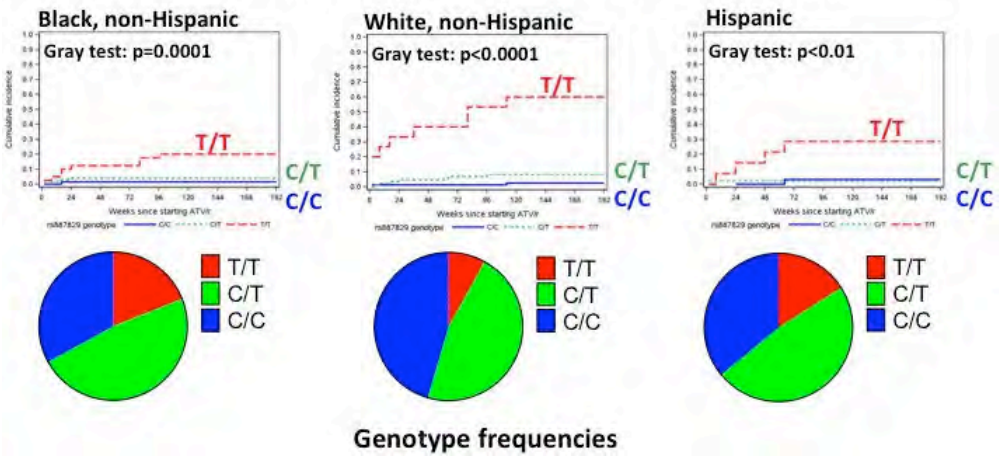
[1]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [2]UCLA Center for Clinical AIDS Research & Education, Los Angeles, CA, US; [3]Emory University School of Medicine, Atlanta, GA, US; [4]Vanderbilt University School of Medicine, Nashville, TN, US

Background: Atazanavir (ATV) increases direct bilirubin (bili) levels which may cause jaundice. Concern about this deters initial prescribing of ATV. AIDS Clinical Trials Group (ACTG) protocol A5257 showed inferior tolerability of ATV/ritonavir (/r) versus both darunavir (DRV)/r and raltegravir (RAL), all with tenofovir/emtricitabine, as initial HIV therapy. We characterized genetic and clinical determinants of premature ATV/r discontinuation for hyperbilirubinemia through 96 weeks, and peak total bili through 24 weeks in A5257.

Methods: Reason for discontinuation was based on site investigator report. Genotypes for rs887829 were by HumanCore Exome Chip. Associations for bili-related ATV/r discontinuation were assessed with a competing risks framework and Cox proportional hazard models. Linear regression models quantified peak total bili associations with *UGT1A1* rs887829, baseline indirect bili, and baseline hemoglobin.

Results: Primary analyses included 481 subjects (211 Black, 183 White, 87 Hispanic) who initiated randomized ATV/r and consented for genetic testing; secondary analyses also included 491 subjects initiating DRV/r and 478 initiating RAL. In the ATV/r group, 14% of subjects were homozygous for rs887829 T/T (19% of Blacks, 8% of Whites, 16% of Hispanics). ATV/r was discontinued for any toxicity or non-toxicity reason in 30%, 8% bili-related. Bili-related ATV/r discontinuation was associated with rs887829 T/T (**Figure**). Positive predictive values of rs887829 T/T for bili-related ATV/r discontinuation were 20% in Blacks; 60% in Whites, 29% in Hispanics; Negative predictive values were 97%, 95% and 97%, respectively. With rs887829 T/T, median peak total bili was 4.9 mg/dL (IQR=2.0-7.2 mg/dL) in Blacks, 4.6 mg/dL (IQR=1.3-7.4 mg/dL) in Whites, and 3.4 (IQR=0.9-4.7 mg/dL) in Hispanics. In multivariable models, rs887829 T/T and baseline bili were independently associated with peak total bili, but only rs887829 T/T was associated with bili-related ATV/r discontinuation. In subjects with rs887829 C/C genotypes, ATV/r tolerability was non-inferior to DRV/r, but was still inferior to RAL.

Figure. Bilirubin-related ATV/r Discontinuation and rs887829



Conclusions: Without rs887829 T/T, likelihood of bili-related ATV/r discontinuation was low. With rs887829 T/T, likelihood of bili-related ATV/r discontinuation varied by race/ethnicity, despite similar bili levels. Genetic testing to avoid ATV/r prescribing with rs887829 T/T would improve ATV/r tolerability and reduce likelihood of bili-related ATV/r discontinuation.

516 ABCB1 Polymorphism Affects Tenofovir Exposure as Determined by Areas-Under-the-Time-Concentration-Curve With 24-hour Intensive Pharmacokinetic Monitoring

Sanjiv M. Baxi[1]; Peter Bacchetti[1]; Mardge Cohen[2]; Jack A. Dehovitz[3]; Kathryn Anastos[4]; Stephen J. Gange[5]; Mary A. Young[6]; Monica Gandhi[1]; Bradley Aouizerat[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]John Stroger (formerly Cook County) Hospital, Chicago, IL, US; [3]State University of New York Downstate Medical Center, Brooklyn, NY, US; [4]Montefiore Medical Center, University Hospital for Albert Einstein College of Medicine, Bronx, NY, US; [5]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [6]Georgetown University, Washington, DC, US

Background: Although tenofovir (TFV) is commonly used in HIV treatment and prevention, pharmacogenomic studies of this agent are limited. Modeling of genetic factors with other determinants of exposure is important. We performed intensive pharmacokinetic (iPK) studies in a diverse cohort of HIV-infected women and identified single nucleotide polymorphisms (SNPs) in genes associated with tenofovir (TFV) metabolism. Models with genetic and non-genetic factors were fit to fully assess contributors to TFV exposure.

Methods: The Women's Interagency HIV Study (WIHS) is a multicenter, prospective cohort of representative HIV-infected women. Participants on TFV-based therapy underwent 24-hour iPK sampling after a witnessed dose under steady-state conditions. Factors that affect PK were measured, including race, age, ritonavir (RTV) use, baseline kidney function (by estimated GFR via serum creatinine) and weight. Participant areas under the time concentration curve (AUCs) were calculated using the trapezoidal rule. Genetic data were collected on all participants. SNPs with an allele frequency of >0.05 were screened in three genes identified as important in the PK of TFV, specifically the ATP-binding cassette (ABC) B1, ABCC2 and organic anion transporter 1 (OAT1). Each SNP was evaluated as a single addition to an established model with non-genetic factors.

Results: Of 93 participants, 61% were African-American, 60.2% used RTV, and 9.7% had an eGFR <70 mL/min. Median (range) TDF AUC was 3340 (1026-9356) ng × h/ml and BMI 27 (15-62) kg/m^2. None of 88 SNPs met our a priori p<0.001 threshold for association with TDF AUC in multivariate modeling; rs4728707 in ABCB1 (CC versus CA; 8.1% allele frequency, no AA) had the smallest observed p-value (1.29 fold effect, 95% CI 1.02, 1.63; p=0.03). Of non-genetic factors, increasing BMI was associated with lower log TDF AUC, while age, ritonavir use and baseline eGFR were associated with higher log TDF AUC (**Table**). Due to non-normality of residuals, we repeated the model using robust standard errors and rs472870 had CI 1.09 to 1.54 with p=0.004.

Factor	Effect on log AUC (+95% CI)	p-value
Age (per 10 years)	**1.16 (1.05, 1.29)**	0.006
BMI (per 10 percent increase)	**0.96 (0.93, 0.99)**	0.01
Ritonavir use vs not	**1.26 (1.06, 1.49)**	0.01
African-American vs other	**1.04 (0.87, 1.25)**	0.67
eGFR < 70 vs > 70	**1.38 (1.00, 1.91)**	0.05
rs4728707 (CC versus CA)	**1.29 (1.02, 1.63)**	0.03

Multivariate Model Assessing Factors Associated with TDF AUC (n=93).

Conclusions: A comprehensive evaluation of 88 SNPs spanning three genes associated with TFV exposure assessed in multivariate models with non-genetic factors identified no strong associations, but ABCB1 rs4728707 had an estimated 29% increase in tenofovir AUC in 24 hour iPK monitoring. Genetic evaluations in real-world populations may help define optimal strategies to maximize efficacy and minimize toxicity for treated individuals.

517 Pharmacogenomics of Plasma Tenofovir Clearance and Change in Creatinine Clearance

Valentine Wanga[1]; Charles Venuto[2]; Gene D. Morse[3]; Edward A. Acosta[5]; Eric Daar[4]; David W. Haas[1]; Chun Li[1]; Bryan E. Shepherd[1]

[1]Vanderbilt University School of Medicine, Nashville, TN, US; [2]University of Rochester Medical Center, Rochester, NY, US; [3]State University of New York at Buffalo, Buffalo, NY, US; [4]Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, US; [5]University of Alabama at Birmingham, Birmingham, AL, US

Background: Candidate gene studies have reported associations between single nucleotide polymorphisms (SNPs, e.g. *ABCC2* -24T⟶C, rs717620) and renal toxicity with tenofovir (TFV) disoproxil fumarate (TDF). We performed genome-wide association analyses of plasma TFV clearance, and change in creatinine clearance (CrCl) in AIDS Clinical Trails Group protocol A5202.

Methods: In A5202, 1858 HIV-infected subjects were randomized to double-blinded TDF/emtricitabine or abacavir (ABC)/lamivudine, with either open-label atazanavir/ritonavir or efavirenz. Plasma TFV clearance was estimated from a nonlinear mixed-effects approach. Serum CrCl was determined before entry, at entry, at weeks 4, 8, 16 and 24, and every 12 weeks thereafter. Illumina Human1M-Duo (~1.2 million SNPs) genotypes were from a separate project. TFV clearance analyses included 501 subjects randomized to TDF arms, and CrCl analyses included 1096 subjects randomized to TDF or ABC arms, all with genotype data. Multivariable regression models tested for associations between SNPs and TFV clearance and 6-month CrCl change. ABC arms were included in CrCl analyses as a control to identify SNPs associated with differential CrCl change with TDF, based on a test for interaction. In addition to genome-wide analyses, for TFV clearance we considered all SNPs in 11 candidate genes, and 18 PharmGKB SNPs. For CrCl change we also considered 77 SNPs associated with renal phenotypes in the GWAS Catalog.

Results: Median CrCl at baseline was 116 ml/min (IQR 100 to 136). Median CrCl change at 6 months in TDF and ABC arms was -0.5 mL/min (-10.7 to +10.8) and +2.2 (IQR -9.9 to +13.2), respectively. Correcting for multiple comparisons, no SNP was associated with plasma TFV clearance or differential CrCl change between TDF and ABC arms, respectively. In TFV clearance candidate gene analysis, most SNPs evaluated were in *ABCC4*. In the *ABCC4* region, the lowest p-value was in *CLDN10* (rs12866697, P=1.4x10^{-3}). Among African Americans, *SLC22A2* rs3127573 was associated with a positive 6-month CrCl change (P = 3.3x10^{-5}). Previously reported SNPs (e.g. *ABCC2* -24T⟶C) were not associated with CrCl change at nominal significance.

Conclusions: Among A5202 participants randomized to TDF/emtricitabine-containing regimens, no SNP was genome-wide associated with plasma TFV clearance or with differential 6-month CrCl change between TDF and ABC arms. We did not replicate SNPs previously associated with TDF renal toxicity.

518 Variant ITPA Phenotypes Are Associated With Increased Ribavirin Triphosphate Levels

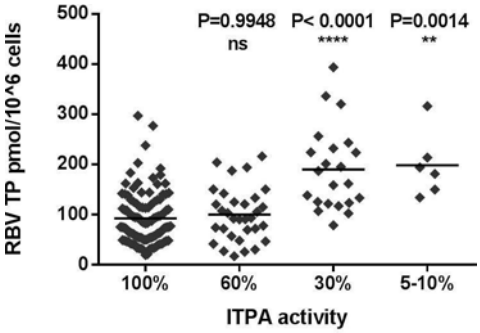
Leah C. Jimmerson[1]; Thomas J. Urban[2]; Eric Meissner[3]; Ariel Hodara[1]; Jacob A. Langness[4]; Christina Aquilante[1]; Aimee Truesdale[5]; Fafa Baouchi-Mokrane[5]; Michelle Ray[1]; Jennifer J. Kiser[1]

[1]University of Colorado, Aurora, CO, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]NIAID, NIH, Bethesda, MD, US; [4]University of Colorado Health, Aurora, CO, US; [5]Denver Health and Hospital Authority, Denver, CO, US

Background: Single nucleotide polymorphisms (SNPs) in the rs1127354 and/or rs7270101 genes encoding the inosine triphosphatase (ITPA) enzyme provide protection against ribavirin (RBV)-induced hemolytic anemia. The effect of these SNPs on the active triphosphate (TP) form of RBV has not been assessed. We sought to determine if there was an association between ITPA genetics and RBV TP concentrations in red blood cells (RBC).

Methods: RBC were collected from individuals receiving RBV-based HCV treatment. RBV TP concentrations were determined in RBC or dried blood spots using a validated LC-MS/MS assay linear in the range of 0.5-200 pmol/sample, then normalized to cell count (pmol/106 cells). Genotyping of ITPA SNPs was performed using the ABI TaqMan allelic discrimination kit and the BIO-RAD CFX Connect Real-Time PCR Detection System using standard TaqMan Universal PCR conditions. ITPA phenotypes were defined as 100%, 60%, 30%, and 5-10% activity. ANOVA was used for overall comparison between ITPA phenotypes with individual t-tests for differences relative to 100% activity.

Results: RBC were obtained from 186 individuals [60% male, 63% white/29% African American, median (range) age and weight of 53 (21, 78) years and 85 (45, 153) kg] receiving RBV for a median (range) of 84 (19, 336) days. RBV TP was significantly different between ITPA phenotypes (figure, p<0.0001), with RBV-TP in the 30% and 5-10% activity phenotypes being approximately 2-fold higher than wild-type (100%).



Conclusions: ITPA variant phenotypes have higher RBV TP concentrations in RBC despite having less RBV-induced hemolytic anemia. A potential mechanism for this observation is that ITPA may degrade RBV TP in RBC and thus phosphorylated RBV levels are higher in subjects with ITPA variant phenotypes. Prospective studies are needed to confirm and extend these findings, to establish the mechanism, and to evaluate additional cell types other than RBC.

TUESDAY, FEBRUARY 24, 2015

Session P-H3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Drug-Drug Interactions

519 Interactions of Antiretroviral Drugs With the SLC22A1 (OCT1) Drug Transporter

Darren M. Moss; Neill Liptrott; Marco Siccardi; Andrew Owen

University of Liverpool, Liverpool, United Kingdom

Background: SLC22A1 is expressed on the basolateral membrane of hepatic liver cells and is involved in the excretion of numerous cationic drugs into the bile. The inhibition of SLC22A1 by several antiretrovirals, such as the protease inhibitor darunavir, has not previously been determined. In order to better understand and predict drug-SLC22A1 interactions, a range of antiretrovirals were screened for SLC22A1-associated inhibition and transport.

Methods: Stable SLC22A1-expressing KCL22 cells were produced previously by nucleofection and neomycin selection. Control KCL22 cells were transfected with the empty vector pcDNA3.1. Accumulation of 14C radiolabelled tetraethylammonium (TEA; 5.4 μM, 0.3 μCi/mL, 30 min) was determined in SLC22A1-expressing and mock-transfected cells with and without 50 μM of control SLC22A1 inhibitors prazosin or cepharanthine, or 50 μM of each antiretroviral drug. Following the experiment, SLC22A1 IC_{50} values for efavirenz, darunavir and prazosin were determined (inhibitor range 0-100 μM). Cellular accumulation of efavirenz and darunavir (1 μM) was also assessed in SLC22A1-expressing KCL22 cells and reversibility was assessed using the SLC22A1-inhibitor, prazosin (200 μM).

Results: TEA accumulation was higher in SLC22A1-expressing cells compared to mock-transfected cells (10.5 ± 0.6 μM versus 0.3 ± 0.004 μM, p<0.001) and was significantly reduced in SLC22A1-expressing cells when co-incubated with all antiretrovirals tested except atazanavir, lamivudine, tenofovir, zidovudine and raltegravir (Table). SLC22A1 IC_{50} values in the presence of 10% FBS for efavirenz, darunavir and prazosin were 21.8, 46.2 and 2.8 μM, respectively. Efavirenz accumulation was higher in SLC22A1-expressing cells compared to mock-transfected cells (16.3% higher, p<0.05) which was reversed using prazosin, whereas no difference was observed for darunavir (p=0.45).

Drug class	Inhibitor	TEA concentration (μM ± SD)	P value
n/a	None	10.5 ± 0.6	n/a
	Mock transfected	0.3 ± 0.004	**<0.001**
Control SLC22A1 inhibitor	Prazosin	2.1 ± 0.4	**<0.001**
	Cepharanthine	2.4 ± 0.2	**<0.001**
Protease inhibitor	Atazanazir	10.2 ± 0.8	0.649
	Lopinavir	7.2 ± 1.8	**0.018**
	Amprenavir	6.8 ± 1.6	**0.007**
	Indinavir	5.2 ± 0.6	**<0.001**
	Darunavir	4.7 ± 0.4	**<0.001**
	Ritonavir	4.0 ± 0.3	**<0.001**
	Nelfinavir	3.1 ± 2.5	**0.033**
Nucleoside reverse transcriptase inhibitor	Lamivudine	11.4 ± 0.6	0.083
	Tenofovir	9.7 ± 0.6	0.158
	Zidovudine	8.5 ± 3.1	0.390
	Zalcitabine	9.1 ± 0.7	**0.042**
	Abacavir	8.8 ± 0.8	**0.027**
	Stavudine	7.6 ± 0.6	**0.001**
Non-nucleoside reverse transcriptase inhibitor	Etravirine	8.2 ± 1.4	**0.032**
	Neviripine	8.0 ± 1.5	**0.026**
	Rilpivirine	6.3 ± 0.2	**<0.001**
	Efavirenz	5.4 ± 0.7	**<0.001**
Integrase inhibitor	Raltegravir	9.6 ± 1.4	0.340

Conclusions: Numerous antiretrovirals showed inhibition of SLC22A1 *in vitro*. Particularly noticeable was the predominance of SLC22A1 inhibitors in the protease inhibitor and non-nucleoside reverse transcriptase inhibitor classes. Maximum patient plasma concentrations of efavirenz (12.9 μM) and darunavir/r (11.9 μM) are lower than the SLC22A1 IC_{50}s determined. Efavirenz showed moderately higher but statistically significant accumulation in SLC22A1-expressing cells. These data inform the mechanistic basis for disposition, drug-drug interactions and pharmacogenetic candidate gene selection for antiretroviral drugs.

520 EFV but Not ATV/r Significantly Reduces Atovaquone Concentrations in HIV+ Subjects

Monica M. Calderon[4]; Joseph A. Kovacs[2]; Alice K. Pau[2]; Maryellen McManus[2]; Raul Alfaro[1]; Parag Kumar[1]; Scott R. Penzak[3]

[1]*National Institutes of Health (NIH), Bethesda, MD, US;* [2]*National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US;* [3]*University of North Texas System College of Pharmacy, Forth Worth, TX, US;* [4]*US Food and Drug Administration (FDA), Silver Spring, MD, US*

Background: Atovaquone is an alternative agent for prophylaxis and treatment of PCP and toxoplasmosis. Previous studies have shown that average steady state atovaquone concentrations (C_{avg}) ≥14 μg/mL and ≥18.5 μg/mL are predictive of successful treatment of PCP and toxoplasmosis, respectively. In a recent study, atovaquone exposure following a single dose of atovaquone/proguanil was reduced by 46-75% in HIV+ patients receiving EFV, LPV/r or ATV/r compared to HIV- controls receiving no ART. The current study was conducted to determine if similar pharmacokinetic (PK) interactions occur in HIV+ subjects receiving atovaquone oral suspension at doses used in the treatment of PCP or toxoplasmosis.

Methods: 30 HIV+ volunteers were recruited, 10 each taking EFV-based ART, ATV/r-based ART, or no ART. Subjects were randomly assigned to atovaquone 750 mg BID with food for 14 days (Phase 1) followed (after a washout period) by atovaquone 1500 mg BID with food for 14 days (Phase 2), or vice versa. On day 14 of each phase, blood samples were collected over 12 hrs to determine atovaquone PK parameter values including area under the concentration-time curve [AUC_t] and C_{avg} using non-compartmental methods. PK parameter values from the EFV and ATV/r arms were compared to the no ART arm using an unpaired t-test.

Results: 29 of 30 subjects (25 males; mean age: 42±11 yrs) completed both dosing cohorts. HIV-RNA was < 50 copies/mL in all subjects in the EFV and ATV/r-based ART groups. Median (range) HIV-RNA in the no ART group was 1224 (<40-26,743) copies/mL. Median (range) CD4+ counts in the EFV, ATV/r, and no ART-based groups were 602 (212-1321), 616 (357-916), and 585 (412-912) cells/mm^3, respectively. Geometric means with 90% CIs are presented for AUC_t and C_{avg}. Geometric mean ratios (GMR) are also included for EFV vs. no ART, and ATV/r vs. no ART.

Atovaquone 750 mg twice daily x 14 days					
	Concurrent EFV	**Concurrent ATV/r**	**No Concurrent ARVs (Control)**	**GMR (EFV: Control)**	**GMR (ATV/r: Control)**
AUC_t (μg*hr/mL) 90% CI *P* vs Control	178 (157-198) 0.001	306 (231-380) 0.4	364 (296-432)	0.53 (0.43 - 0.64)	0.90 (0.67 - 1.21)
C_{avg} (μg/mL) 90% CI *P* vs Control	14.8 (13.1-16.5) 0.001	25.5 (19.3-31.7) 0.4	30.3 (24.6-36.0)	0.53 (0.43 - 0.64)	0.90 (0.67 -1 .21)
Atovaquone 1500 mg twice daily x 14 days					
AUC_t (μg*hr/mL) 90% CI *P* vs Control	256 (237-274) 0.01	431 (327-535) 0.8	455 (351-558)	0.56 (0.43 – 0.73)	0.95 (0.65 – 1.38)
C_{avg} (μg/mL) 90% CI *P* vs. Control	21.3 (19.7-22.9) 0.01	35.9 (27.2-44.6) 0.8	37.9 (29.2-46.5)	0.56 (0.43 – 0.73)	0.95 (0.65 – 1.38)

Atovaquone PK alone, and in combination with ATV/r or EFV in HIV+ Volunteers

Conclusions: Subjects on EFV-based ART had 47% and 44% lower atovaquone exposure than no ART subjects at atovaquone doses of 750 mg BID and 1500 mg BID, respectively ($P \leq 0.01$ for each). Moreover, 4 of 10 subjects (40%) on EFV-based ART + atovaquone 750 mg BID had an atovaquone C_{avg} <14 μg/mL – the concentration associated with successful PCP treatment. In contrast, ATV/r PK parameter values did not differ significantly from control group values at either of the studied doses. These data suggest that the current recommended dose of atovaquone 750 mg BID for PCP treatment may not be adequate in all patients receiving concurrent EFV.

521 The Effect of Single and Multiple Dose Rifampin on the Pharmacokinetics of Doravirine

Ka Lai Yee[3]; Sauzanne G. Khalilieh[2]; Rachael Liu[3]; Rosa Sanchez[3]; Matt S. Anderson[4]; Candice Smith-Bradley[5]; Joan Butterton[6]; Timothy Judge[1]; Helen Manthos[1]; John Brejda[1]

[1]*Celerion, Lincoln, NE, US;* [2]*Merck and Co, Inc, Kenilworth, NJ, US;* [3]*Merck and Co., Inc., West Point, PA, US;* [4]*Merck and Co, Inc, Rahway, NJ, US;* [5]*Merck and Co, Inc, Upper Gwynedd, PA, US;* [6]*Merck and Co, Inc, Boston, MA, US*

Background: Doravirine is a novel, potent, HIV-1 non-nucleoside reverse transcriptase inhibitor that is primarily metabolized by oxidation via CYP3A4. Based on in vitro data, doravirine is a substrate of P-gp but not of OATP1B1. This study assessed the impact of single dose (SD) and multiple dose (MD) rifampin administration on the pharmacokinetics (PK) of doravirine. After multiple dosing, rifampin is a strong inducer of CYP3A4, while SD administration of rifampin was performed to assess the effects of hepatic OATP1B1 inhibition and intestinal P-gp inhibition on the absorption and metabolism of doravirine.

Methods: This was an open-label, 2-period, fixed-sequence study in healthy adult men (n=11). In Period 1, a SD of 100 mg doravirine was administered on Day 1. In Period 2, following a 7-day washout, a SD of 600 mg rifampin and 100 mg doravirine were coadministered on Day 1. Following a 3-day washout, 600 mg rifampin was administered once daily for 15 days (Days 4-18) and 100 mg doravirine was coadministered on Day 17. Safety evaluations were performed throughout the study.

Results: There were no serious clinical or laboratory adverse experiences (AEs) and all reported AEs were judged as mild in intensity. Following coadministration of single doses of rifampin and doravirine, the geometric mean ratio (GMR) (90% confidence interval [CI]) (doravirine + SD rifampin/doravirine) for AUC0-∞ and C24 were 0.91 (0.78, 1.06) and 0.90 (0.80, 1.01), respectively, suggesting that OATP1B1 inhibition does not impact the PK of doravirine. The GMR (90% CI) for Cmax were 1.40 (1.21, 1.63), indicating that P-gp inhibition may increase doravirine Cmax. After coadministration with multiple doses of rifampin, doravirine concentrations were significantly reduced as expected based on the role of CYP3A4 in doravirine metabolism. The GMRs (doravirine + MD rifampin/doravirine) and 90% CIs for AUC0-∞, C24, and Cmax were 0.12 (0.10, 0.15), 0.03 (0.02, 0.04), and 0.43 (0.35, 0.52), respectively.

Conclusions: Doravirine was generally well tolerated when administered alone or with rifampin. Inhibition of OATP1B1 and P-gp by SD rifampin did not have a clinically meaningful effect on the PK of doravirine. Multiple dosing of rifampin significantly reduced doravirine AUC0-∞, Cmax and C24. Thus, doravirine should not be administered with strong CYP3A4 inducers.

522 Drug-Drug Interaction Between HCV Inhibitors Grazoprevir/Elbasvir With Dolutegravir

Wendy W. Yeh[1]; Ted Marenco[2]; Hwa-Ping Feng[1]; Zifang Guo[1]; Daria Stypinski[2]; Lisa Ross[3]; Ivy H. Song[4]; Patricia Jumes[1]; Barbara Cook[2]; Joan R. Butterton[1]
[1]Merck & Co, Inc, Boston, MA, US; [2]Celerion, Lincoln, NE, US; [3]ViiV Healthcare, Research Triangle Park, NC, US; [4]GlaxoSmithKline, Research Triangle Park, NC, US

Background: Grazoprevir (MK-5172) is a potent, once-daily inhibitor of the hepatitis C virus (HCV) NS3/4A protease and elbasvir (MK-8742) is a potent, once-daily HCV NS5A replication complex inhibitor that are being developed as a fixed-dose combination therapy for the treatment of chronic HCV infection in mono- and HCV/human immunodeficiency virus (HIV)-coinfected patients. This study evaluated the safety and pharmacokinetic (PK) interactions of grazoprevir and elbasvir when coadministered with dolutegravir (DTG), a HIV-1 integrase strand transfer inhibitor in healthy volunteers.

Methods: This was an openlabel, 2period, fixedsequence study in 12 healthy adult males and females. In period 1, a single dose (SD) of 50 mg DTG was administered, followed by a 3-day washout. In period 2, 200 mg grazoprevir + 50 mg elbasvir were administered once daily on days 111, with a SD of 50 mg DTG coadministered on day 9. PK assessments for DTG were performed on day 1 of period 1 and day 9 of period 2, and for grazoprevir and elbasvir on days 8 and 9 of period 2. Safety assessments included electrocardiograms, vital signs, clinical laboratory tests, physical examination, and adverse event (AE) monitoring.

Results: Grazoprevir + elbasvir had no clinically meaningful effect on the DTG PK, with $AUC_{0-\infty}$ and C_{24} geometric mean ratios (GMRs) (90% confidence intervals [CIs]) of 1.16 (1.00, 1.34) and 1.14 (0.95, 1.36), respectively. Similarly, the elbasvir PK were not affected by coadministration of DTG, with AUC_{0-24}, C_{max}, and C_{24} GMRs (90% CIs) of 0.98 (0.93, 1.04), 0.97 (0.89, 1.05), and 0.98 (0.93, 1.03), respectively. However, DTG did result in decreased grazoprevir PK with AUC_{0-24}, C_{max}, and C_{24} GMRs (90% CIs) of 0.81 (0.67, 0.97), 0.64 (0.44, 0.93), and 0.86 (0.79, 0.93), respectively. Coadministration of grazoprevir + elbasvir with DTG was generally well tolerated in the healthy subjects. The most common drug-related AEs were dyspepsia, headache, and sinus congestion, which were mild and resolved by study end.

Conclusions: Coadministration of grazoprevir + elbasvir with DTG had no clinically meaningful effect on the PK of DTG or elbasvir. Coadministration of DTG with grazoprevir + elbasvir decreased grazoprevir PK. However, the decrease in grazoprevir PK was within the therapeutic window currently defined for grazoprevir. These results suggest that no dose adjustments in grazoprevir, elbasvir, or DTG are needed for coadministration in coinfected patients.

523 HIV-1 Attachment Inhibitor Prodrug BMS-663068: Interactions with DRV/r and/or ETR

Ishani Savant Landry; Xiaolu Tao; Jeffrey Anderson; Michael Hesney; Michele Stonier; Susan Lubin; Jian Wang; George J. Hanna; David W. Boulton
Bristol-Myers Squibb, Princeton, NJ, US

Background: BMS-663068 is a prodrug of BMS-626529, a first-in-class attachment inhibitor that binds directly to HIV-1 gp120, preventing initial viral attachment and entry into host CD4+ T-cells. Phase 2b data (through Week 24) show BMS-663068 has similar efficacy to ATV/r (both combined with RAL+TDF) in treatment-experienced (TE), HIV-1-infected subjects (sbj). Darunavir/ritonavir (DRV/r) and etravirine (ETR) use is common among TE patients. As the CYP3A4 metabolic pathway contributes to the metabolism of BMS-626529, and DRV/r and ETR are also metabolized by or alter CYP3A4 activity, there is potential for drug-drug interactions.

Methods: AI438020 was an open-label, single-sequence, multiple-dose, three cohort study in 42 healthy sbj (n=14 per cohort). BMS-663068 was given at 600mg BID (A), DRV/r at 600mg/100mg BID (B), and ETR at 200mg BID (C). Dosing in each cohort was on Days 1–4, 7–16, and 17–26, with a 2-day washout (WO) on Days 5 and 6. Treatment order in each cohort was: Cohort 1: A (WO), then B, followed by A+B; Cohort 2: A (WO), then C, followed by A+C; Cohort 3: A (WO), then B+C, followed by A+B+C. PK parameters were derived using non–compartmental methods. Geometric mean ratios and 90% confidence intervals (CI) were calculated from log-transformed C_{max}, AUC_{tau}, and C_{12} using mixed-effect modeling, with limits of 0.75–1.70 and 0.8–1.25 predefined for ETR and DRV/r, and BMS-663068 use respectively. Safety measurements included vital signs and adverse event monitoring.

Results: Compared to BMS-663068 BID alone, co-administration with DRV/r increased BMS-626529 C_{max}, AUC_{tau}, and C_{12} by ~50%, ~60%, and ~90%, respectively, consistent with CYP3A inhibition by ritonavir (RTV). ETR decreased BMS-626529 C_{max}, AUC_{tau}, and C_{12} each by ~50%, consistent with CYP3A induction by ETR. DRV/r + ETR increased BMS-626529 C_{max}, AUC_{tau}, and C_{12} by ~50%, ~30%, and ~30%, respectively, consistent with RTV inhibition of CYP3A predominating over ETR induction (Table). Conversely, BMS-626529 caused minimal changes to the PK of DRV/r, ETR or DRV/r + ETR, and were within predefined no-effect limits. BMS-663068 was generally well tolerated. Skin rash (Grade 1–2) was reported in 28.3% of sbj and considered related to ETR and DRV/r, not to BMS-663068.

Treatment and Comparison [n]		PK parameter, adjusted geometric means		
		C_{max} ng/mL (90% CI)	AUC_{tau}, ng.h/mL (90% CI)	C_{12}, ng/mL (90% CI)
Cohort 1	BMS-663068 [14]	2033 (1619, 2553)	12632 (10142, 15735)	308 (213, 444)
	BMS-663068 + DRV/r [12]	3098 (2386, 4022)	20633 (16333, 26065)	577 (455, 732)
		C_{max} ratio	**AUC_{tau} ratio**	**C_{12} ratio**
	BMS-663068 + DRV/r versus BMS-663068	1.524 (1.279, 1.815)	1.633 (1.423, 1.875)	1.875 (1.093, 3.216)
Cohort 2	BMS-663068 [14]	1941 (1699, 2219)	13364 (11574, 15430)	479 (310, 740)
	BMS-663068 + ETR [14]	1003 (858, 1171)	6714 (5815, 7753)	231 (156, 344)
		C_{max} ratio	**AUC_{tau} ratio**	**C_{12} ratio**
	BMS-663068 + ETR versus BMS-663068	0.516 (0.454, 0.587)	0.502 (0.442, 0.571)	0.483 (0.324, 0.720)
Cohort 3	BMS-663068 [18]	1568 (1362, 1805)	10339 (9136, 11700)	312 (221, 441)
	BMS-663068 + DRV/r + ETR [18]	2398 (2144, 2682)	13861 (11659, 16478)	416 (286, 603)
		C_{max} ratio	**AUC_{tau} ratio**	**C_{12} ratio**
	BMS-663068 + DRV/r + ETR versus BMS-663068	1.529 (1.323, 1.768)	1.341 (1.172, 1.534)	1.332 (0.980, 1.809)

PK results of BMS-626529 when coadministered with DRV/r and/or ETR

Conclusions: BMS-663068 can be co-administered with DRV/r or DRV/r + ETR, without dose adjustment. Co-administration with ETR (without DRV/r) resulted in a ~50% decrease in BMS-626529 C_{12} levels. Skin rash was consistent with ETR and DRV/r administration.

THURSDAY, FEBRUARY 26, 2015

Session P-H4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Pharmacokinetics in Compartments and Reservoirs and of Novel Formulations

524 Local and Systemic Pharmacokinetic Profile of Dapivirine Vaginal Ring-004 When Used Continuously Over Various Periods up to Twelve Weeks

Annalene M. Nel[1]; Wouter Haazen[2]; Marisa Russell[1]; Jeremy P. Nuttall[3]; Neliette Van Niekerk[1]; Nicoline Treijtel[4]

[1]International Partnership for Microbicides, Paarl, South Africa; [2]SGS Life Science Services, Antwerp, Belgium; [3]International Partnership for Microbicides, Silver Spring, MD, US; [4]Kinesis Pharma BV, Breda, Netherlands

Background: Dapivirine Vaginal Ring-004 (25 mg dapivirine) is a topical microbicide being evaluated for safety and efficacy in a Phase III clinical program. The pharmacokinetic (PK) profile of Ring-004 has been described for up to 35 days of continuous use. This trial investigated the PK of dapivirine from Ring-004 for continuous use up to 12 weeks.

Methods: An open-label, parallel group trial was conducted among 40 healthy, HIV-negative women, aged 18-40 years. Participants were divided into 5 groups of 8 women each: participants in Group A kept the ring inserted for 1 week, Group B for 2 weeks, Group C for 4 weeks, Group D for 8 weeks and Group E for 12 weeks. Dapivirine concentrations were determined in plasma and vaginal fluid (CVF) samples collected by tear test strip at the cervix, and residual dapivirine levels were assessed in used rings.

Results: Mean plasma dapivirine C_{max} was similar across groups: 385 to 449 pg/mL. Median t_{max} was variable and ranged from 7 days to 17.5 days. Mean $C_{prior\ to\ ring\ removal}$ was similar for rings inserted for 1, 2 or 4 weeks (329 to 379 pg/mL), and showed a pronounced decline for longer ring use: 228 pg/mL at Week 8; 156 pg/mL at Week 12. Maximum dapivirine CVF concentrations were achieved after approximately 1 week, displaying high inter- and intra-individual variability. Mean C_{max} ranged between 48.2 and 61.3 μg/g across groups. Mean $C_{prior\ to\ ring\ removal}$ was similar for rings inserted for 1 or 2 weeks (39.5 and 44.6 μg/g), and then declined with duration of ring use: 20.1 μg/g at Week 4; 17.2 μg/g at Week 8; 13.3 μg/g at Week 12. The lowest concentration observed (Week 12) was 1.1 μg/g, which was well above the in vitro IC_{99} in cervical tissue (3.3 ng/mL). Mean ring residual levels of dapivirine were 16.8, 21.6, 20.1, 17.0 and 15.0 mg for Groups A to E. In general, ring residual levels decreased with duration of ring use; results for Groups A and B should be interpreted with caution due to problems with validation of analytical results for these rings. No product-related SAEs occurred. Three AEs of vaginal discharge (Grade 1) and one AE of bacterial vaginitis (Grade 2) were reported as product-related.

Conclusions: Dapivirine ring residual levels, and plasma and CVF concentrations decreased with the duration of ring use for periods of greater than 4 weeks; mean CVF concentrations at 12 weeks were >4000 times above IC_{99}. Ring-004, when worn continuously up to 12 weeks, was well tolerated with no safety concerns.

525 Steady-state TDF/FTC in Genital, Rectal, and Blood Compartments in Males vs Females

Sharon M. Seifert[1]; Amie L. Meditz[2]; Jose R. Castillo-Mancilla[3]; Edward M. Gardner[3]; Brandon Klein[1]; Becky Kerr[1]; L. Anthony Guida[1]; Jia-Hua Zheng[1]; Lane R. Bushman[1]; Peter L. Anderson[1]

[1]University of Colorado, Aurora, CO, US; [2]Boulder Community Hospital, Boulder, CO, US; [3]University of Colorado School of Medicine, Aurora, CO, US

Background: Despite the widespread use of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) for treatment and prevention of HIV infection, gaps in knowledge remain regarding the pharmacokinetics (PK) of the intracellular active moieties, tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP), at steady-state concentrations

(Css) in different compartments in the body. The purpose of this study was to describe the steady-state PK of TFV-DP and FTC-TP in genital, rectal, and blood compartments in HIV-positive and negative males and females.

Methods: HIV-positive and negative adults were enrolled in an intensive PK study of daily TDF/FTC for 30 days. Peripheral blood mononuclear cells (PBMC) were obtained at first dose, days 3, 7, 20, and 30. Rectal biopsies and genital sampling were performed once each per participant, at staggered visits. Females underwent a cervical brush collection and males provided one semen sample. Cervical cells, seminal leukocytes, and rectal mononuclear cells were isolated, counted, assessed for viability, and lysed. First order PK was used to determine average steady-state values (Css) in each compartment for TFV-DP and FTC-TP. Comparisons were made between the genders and according to HIV status using unpaired t-tests, only for PBMC data given limits on sample sizes.

Results: Thirteen females (10 HIV negative) and 24 males (11 HIV negative) were included. Available samples from female participants included 13 cervical, 10 rectal, and 253 PBMC, and those from males included 18 seminal, 20 rectal, and 414 PBMC. Steady-state was reached in all compartments for both TFV-DP and FTC-TP within 30 days. Css values are shown in the table. TFV-DP and FTC-TP Css in PBMC did not differ significantly by gender or HIV-status, although females trended toward higher concentrations of TFV-DP in PBMC (p=0.08). Females also appeared to have higher TFV-DP in rectal cells. Genital cell concentrations at steady-state were ~10-fold greater in females compared with males for both TFV-DP and FTC-TP.

		Male (n=24)	Female (n=13)
PBMC	TFV-DP fmol/10^6cells	89.9 (73.6 to 106.2)	108 (93.6 to 122.4)
	FTC-TP pmol/10^6cells	5.5 (4.3 to 6.7)	5.6 (4.4 to 6.7)
Genital	TFV- DP fmol/10^6cells	13 (5 to 36)	159 (40 to 602)
	FTC-TP pmol/10^6cells	0.4 (0.2 to 0.7)	5.9 (1.9 to 9.9)
Rectal	TFV- DP fmol/10^6cells	1220 (533 to 2799)	3294 (852 to 11861)
	FTC-TP pmol/10^6cells	1.4 (1.0 to 1.9)	1.4 (0.3 to 2.6)

Css of TFV-DP and FTC-TP in PBMC, genital, and rectal compartments in males and females (mean or point estimate, 95% confidence interval)

Conclusions: These findings illustrate differential drug penetration at steady-state in genital, rectal and blood compartments, which is relevant for prevention of HIV acquisition and suppression of HIV replication within potential reservoirs of the body. Females trended to have higher concentrations in these compartments relative to males. This information provides concentration ranges to help inform dose-response relationships for the prevention and treatment of HIV infection.

526 Effects of Tenofovir/Emtricitabine on Endogenous Deoxyribonucleotide Pools In Vivo

Xinhui Chen[1]; Kevin McAllister[1]; Jia-Hua Zheng[1]; Jose R. Castillo-Mancilla[1]; Amie Meditz[2]; Brandon Klein[1]; Sharon M. Seifert[1]; Lane Bushman[1]; Peter L. Anderson[1]

[1]University of Colorado Anschutz Medical Campus, Aurora, CO, US; [2]Beacon Center of Infectious Diseases, Boulder, CO, US

Background: The potential effects of nucleoside analogs on endogenous deoxyribonucleotides (dNTP) in vivo have not been fully elucidated. The goal of this study was to characterize and quantify the effects of tenofovir-disoproxil fumarate (TDF)/emtricitabine (FTC) therapy on endogenous dNTP pools in HIV-negative and HIV-positive adults.

Methods: Participants were enrolled in a pharmacokinetic study of daily TDF/FTC therapy. Peripheral blood mononuclear cells (PBMC) were collected at baseline (pre-drug), and days 1, 3, 7, 20, and 30 during dosing. HIV-negative adults had visits on days 5, 15, and 30 of drug washout, while HIV-positive adults continued therapy through day 60. The 8 hours post dose samples were used from all on-drug study visits. PBMC were isolated, counted, lysed, and endogenous dNTP including dCTP, dGTP, TTP, and dATP were quantified with validated LC-MS/MS methodology. Comparisons were made with paired t-tests.

Results: 276 PBMC samples were analyzed from 40 participants (21 HIV-negative and 19 HIV-positive); 13 female and 27 male, average age 33 years. 34 subjects completed all study visits, two HIV negative and four HIV-positive subjects stopped early. dNTP were generally (not statistically) higher at baseline in HIV-negative vs HIV-positive participants, with median values of 834 vs 780 (dCTP), 303 vs 244 (dGTP), 475 vs 386 (TTP), and 153 vs 152 (dATP) fmol/10^6 cells. Compared with baseline values, HIV-negative subjects had a reduction of 26% for dCTP (p=0.003), 30% for dGTP (p=0.001), 53% for TTP (p<0.001), and 21% for dATP (p=0.06) by day 3; while corresponding values for HIV-positive subjects were 17% for dCTP (p=0.20), 12% for dGTP (p=0.36), 34% for TTP (p=0.01), and an increase of 9% for dATP (p=0.99). dNTP generally remained below baseline until drug discontinuation. After 5 days of washout in HIV-negative participants, dNTP had essentially returned to baseline values with differences of -6% for dCTP (p=0.33), -14% for dGTP (p=0.16), -1% for TTP (p=0.87), and -11% for dATP (p=0.07).

Conclusions: Endogenous dNTP pools in PBMCs decreased during TDF/FTC therapy, with greater reductions among HIV-negative subjects. These dNTP changes may indicate direct perturbation (eg drug interference with dNTP regulation pathways) and/or indirect perturbation (eg drug-induced reduction of immune activation, in turn reducing dNTP). The effects of lower dNTP on cellular function and antiviral effect should be evaluated in future studies.

527 Higher Cell Accumulation and Antiviral Activity of Lopinavir/Ritonavir Nanoparticles

Philip Martin[1]; Tom O. McDonald[2]; Marco Giardiello[2]; Steven P. Rannard[2]; Andrew Owen[1]

[1]University of Liverpool, Liverpool, United Kingdom; [2]University of Liverpool, Liverpool, United Kingdom

Background: Using an emulsion-templated freeze-drying technique we have synthesised combination lopinavir/ritonavir (LPV/RTV) solid drug nanoparticles (SDNs) with 70% weight drug loading in the dry state and compared their antiretroviral activity and cellular accumulation in primary immune cells.

Methods: MT4 cells (NIBSC, UK) and primary immune cells (CD4+ T lymphocytes, CD56+ natural killer cells, CD14+ monocytes and monocyte-derived macrophages (MDM)) (Lonza, UK) from 4 donors, were incubated with either combination aqueous solutions or combination solid drug nanoparticle (SDN) suspensions at 10μM lopinavir (LPV; 0.1 μCi H^3) and ritonavir (RTV) at 1:4, 1:8 or 1:40 ratio, for 60 minutes. Aliquots of media (extracellular) and lysed cells (intracellular) were sampled and a cellular accumulation ratio determined. Antiviral activity by combination SDNs and aqueous solutions were assessed against $HIVIII_B$ infected MT4 cells at the same ratios. Data analysis was conducted using GraphPad Prism 3.0 and StatsDirect software.

Results: Cellular accumulation of LPV/RTV SDNs was higher than the equivalent aqueous solution in MT4 (1:4, 1.8-fold, $p < 0.0001$; 1:8, 1.7-fold, $p < 0.0001$ and 1:40; 2.0-fold $p < 0.0001$), CD4+ (1:4; 1.6-fold; $p < 0.0001$, 1:8; 1.7-fold $p < 0.0001$ and 1:40; 2.0-fold $p < 0.0001$), CD14+ (1:4; 1.1-fold; $p = 0.03$, 1:8; 1.2-fold $p = 0.0002$, 1:40; 1.5-fold; $p = 0.0001$), CD56+ (1:4; 1.4-fold; $p < 0.0001$, 1:8; 1.5-fold $p < 0.0001$, 1:40; 1.5-fold $p < 0.0001$) and MDM (1:4; 2.2-fold; $p < 0.0001$, 1:8; 2.3-fold $p < 0.0001$ and 1:40; 2.7-fold $p < 0.0001$).

Activity against $HIVIII_B$ in MT4 cells was higher for SDNs compared to aqueous solutions (1:4, IC_{50} = 10.1 ± 0.5nM versus 15.7 ± 0.3nM, p<0.0001; 1:8, IC_{50} = 14.9 ± 0.6 versus 24.1 ± 1.9nM, p<0.0001; 1:40, IC_{50} = 17.4 ± 0.7 versus 31.7 ± 1.2nM, p<0.0001, respectively) consistent with higher cellular accumulation.

Conclusions: Combination SDNs have increased cellular accumulation and enhanced antiviral activity in cell-based assays. Notably, equivalent protease inhibition *in vitro* with LPV doses requiring 10-fold less RTV was observed. Due to RTV intolerance and long-term toxicities associated with chronic exposure to RTV, strategies to reduce RTV dose are worthy of further investigation.

528 HIV reservoir targeted antiretroviral nanofabrication facilitates viral clearance

Pavan Puligujja[1]; JoEllyn McMillan[1]; Shantanu Balkundi[2]; Prasanta K. Dash[1]; James Hilaire[1]; Santhi Gorantla[1]; Larisa Poluektova[1]; Xin-Ming Liu[1]; Howard Gendelman[1]
[1]*University of Nebraska Medical Center, Omaha, NE, US;* [2]*Kansas University Innovation and Collaboration, Lawrence, KS, US*

Background: Limitations in adherence, toxicity and reservoir targeting underlie the needs for improvements in antiretroviral therapy (ART). We posit that long-acting nanoformulated antiretroviral therapy (nanoART) can address this need by improving current drug pharmacokinetics (PK) and biodistribution. The development of monocyte-macrophage targeting ligands could affect drug depots and target sanctuaries of viral infections. To this end, we developed a folic acid (FA) crystalline nanofabrication for ritonavir-boosted atazanavir (FA-nanoATV/r). The PK and pharmacodynamics properties were, until now, not known.

Methods: The size, shape, zeta potential, and polydispersity of FA poloxamer 407 ATV/r nanoparticles were determined following high-pressure homogenization. NOD/*scid*-IL-2Rγ_c^{null} (NSG) mice were reconstituted with human peripheral blood lymphocytes (hu-PBL) and treated with 10, 50 and 100 mg/kg of native drug, nanoATV/r, FA-nanoATV/r or left untreated. The mice were challenged with $HIV\text{-}1_{ADA}$ (10^4 tissue culture infective dose50, $TCID_{50}$) 24 hrs later and sacrificed 14 days after treatment. In further experiments human CD34+ hematopoietic stem cells (HSC) reconstituted NSG mice at 6-8 weeks age were infected for four weeks with $HIV\text{-}1_{ADA.}$ The mice were then treated every two weeks at week 4, 6 and 8 and sacrificed on week ten post-infection. Bioavailability and tissue biodistribution were determined by ultra performance liquid chromatography-tandem mass spectrometry. Pharmacodynamics was scored by measures of HIV-1p24 levels or viral load determined by immunohistochemistry, reverse transcriptase polymerase chain reaction or by viral RNA copies (Cobas Aplicor V1.5) in spleen, liver, lung or plasma.

Results: FA-nanoATV/r led to an increase in plasma and spleen, liver and lung tissue drug levels up to > 5-fold over uncoated nanoATV/r with protection of CD4+ to CD8+ T cell ratios in Hu-PBL mice. Number of infected HIV-1p24 cells and viral RNA levels in liver, spleen and or lung with FA-nanoATV/r were reduced up to > 2 logs compared to untreated and > 1 log over nanoATV/r treated hu-PBL animals. Two of four HSC NSG mice challenged with $HIV\text{-}1_{ADA}$ showed no detectable virus with the other two demonstrating viral reductions of up to 2 logs.

Conclusions: FA targeted ART nanofabrications are a significant means to improve PK and PD. Reservoir targeting could lead to platforms for chemical viral eradication measures.

529 The Macrophage Proteome Defines the Long Acting Antiretroviral Therapy Cell Depot

Dongwei Guo; Mariluz Araínga; Jayme Horning; Pawel Ciborowski; Xin-Ming Liu; JoEllyn McMillan; Howard Gendelman
University of Nebraska Medical Center, Omaha, NE, US

Background: Long-acting antiretroviral therapy (nanoART) nanoformulations can improve drug adherence, reduce systemic toxicities, and facilitate clearance of human immunodeficiency virus (HIV). While, monocyte-macrophage depots of nanoART are contained in recycling and late endosomes whether these organelles provide strategic advantages for viral elimination is not known.

Methods: We applied quantitative SWATH-MS proteomic and cell profiling to nanoformulated atazanavir (nanoATV) treated $HIV\text{-}1_{ADA}$ infected human monocyte-derived macrophages (MDM). DAVID and KEGG bioinformatics tools were used to define the mechanistic pathways that facilitate cell-nanoATV carriage while limiting viral growth.

Results: Both HIV-1 and nanoATV engaged phagolysosomal trafficking pathways. However, MDM phagolysosomal proteins were dysregulated in opposing directions. Paired-samples Z-test showed that an upregulation of phagolysosomal proteins by HIV-1 was reversed by nanoATV. DAVID and KEGG bioinformatics tools defined the signaling pathways for cell-nanoATV carriage that limiting viral growth. These phagolysosomal protein sets were linked to macrophage functions that included phagocytosis, antigen presentation, secretory activities, phagocytic and cell migration responses. KEGG pathway analyses indicated phagosome signalling as one of the main pathways related to HIV infection and nanoATV treatment. KEGG revealed the up-regulation of Rab5 and -7 proteins in HIV-1 infected cells; in contrast these same proteins were down-regulated in nanoATV-treated HIV-infected cells. Western blot results showed a clear down regulation in the expression of Rab5, 7, 11 and LAMP1 proteins after nanoATV treatment. Measures of reverse transcriptase activity in infected cell treated with nanoATV showed attenuation of viral infection. Cytokine assay detected IL12 and TNF were increased in HIV-1 infected macrophages but reduced with nanoATV treatment.

Conclusions: Late and recycling macrophage endosomes ensure viral replication. These same pathways are nanoART depots. The modulation of phagolysosomal pathways by nanoART in the setting of HIV-1 infection provides a strategic therapeutic advantage enabling viral elimination.

530 Primary CD4 Subsets Are Similarly Loaded by Tenofovir Alafenamide (TAF)

Christian R. Frey; Yang Liu; Darius Babusis; Adam Palazzo; Adrian S. Ray; Michael D. Miller; Kathryn M. Kitrinos; **Christian Callebaut**
Gilead Sciences, Inc., Foster City, CA, US

Background: Tenofovir alafenamide (TAF), a new prodrug of the HIV-1 NRTI tenofovir (TFV), shows improved antiviral activity in monotherapy clinical studies, at lower doses than tenofovir disoproxil fumarate (TDF). TAF delivers TFV more efficiently than TDF to lymphoid cells with a 5-fold increase in intracellular TFV-diphosphate (TFV-DP) level and a 90% reduction in plasma TFV. It had not previously been established that TFV-DP levels are evenly distributed among primary human CD4+ T-lymphocytes (CD4) subsets following TAF treatment. Therefore, intracellular TFV-DP levels were evaluated in CD4 subsets at clinically relevant TAF concentrations.

Methods: In vitro TAF loading studies were conducted using primary cells from healthy human donors. PBMCs, including total CD4, as well as, naïve, effector, central memory and effector memory CD4 T-cell subsets were evaluated. Total CD4 were enriched using magnetic beads and CD4 subsets were isolated by cell sorting based on CD3, CD4, CD45RA, and CCR7 expression. TAF loading was evaluated using a 2h pulse incubation followed by washout and then incubation in drug free media to mimic in vivo TAF exposure. Cell extracts were prepared and TFV, TFV-MP, and TFV-DP levels were measured by LC/MS/MS.

Results: Cell loading studies in PBMCs demonstrated that a 2h pulse and 22h washout of 200-400 nM TAF achieved TFV-DP levels comparable to those observed in vivo following clinical dosing of TAF. There was minimal variation in the levels of intracellular TAF metabolites between donors. Additionally, comparable TFV-DP levels were achieved after a 2h pulse with either 200 or 400 nM TAF in total CD4, as well as in the CD4 subsets, with a trend for higher TFV-DP levels in memory cells compared to other CD4s subsets. For each of the CD4 subsets evaluated, there was no significant decrease in TFV-DP levels at 24h, indicating a uniformly long intracellular half-life in all cell populations, consistent with observations of TFV-DP levels in PBMCs following TAF dosing in clinical studies.

Conclusions: CD4 subsets were similarly loaded by TAF in vitro, achieving high and persistent levels of TFV-DP. The sustained levels of TFV-DP 24h post-treatment suggest that high levels of TFV-DP will be maintained across most relevant CD4 cell subsets in patients receiving TAF. The higher levels in memory subsets may have implications for maintaining viral suppression in latent viral reservoirs and for future cure efforts.

THURSDAY, FEBRUARY 26, 2015

Session P-H5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

New Technologies in Assessing Drug Interactions and Systemic and Intracellular Pharmacology

531 Pharmacokinetic Interactions Between Antidiabetics and Efavirenz Using PBPK Modeling

Catia Marzolini[1]; Rajith Rajoli[2]; Luigia Elzi[1]; Manuel Battegay[1]; David Back[2]; Marco Siccardi[2]

[1]*University Hospital Basel, Basel, Switzerland;* [2]*Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom*

Background: Diabetes has emerged as an important co-morbidity in the aging HIV population. The management of diabetes is complicated by the issue of drug-drug interactions (DDI) between antidiabetics and antiretroviral drugs and the lack of clinical data on how to manage these DDI. The antidiabetics pioglitazone (PIO) and repaglinide (REP) are metabolized by CYP2C8 and CYP3A4 and therefore are subject to DDI with efavirenz (EFV), an inducer of CYP3A4 and inhibitor of CYP2C8. The objective of this study was to simulate the pharmacokinetic (PK) interaction between PIO or REP and EFV using physiologically based pharmacokinetic (PBPK) modeling.

Methods: *In vitro* data describing the physicochemical properties, absorption, distribution, metabolism and elimination of PIO, REP and EFV, as well as the CYP induction and inhibition potential of EFV were obtained from published literature. The experimental data were integrated in a PBPK model developed using Simbiology (Matlab, R2013b), representing molecular, physiological and anatomical processes defining PK. PIO, REP and EFV plasma profiles were simulated in 50 virtual individuals receiving either PIO 15 mg once daily (QD) or REP 2 mg thrice daily (TID) with or without EFV 600 mg QD for 14 days. Dose adjustments of PIO and REP were simulated to overcome the DDI with EFV.

Results: Simulated PK parameters were in agreement with observed clinical data. Simulated versus observed mean AUC and Cmax (± SD) were: 3699 (1413) vs 5020 (1070) ng.h/ml and 535 (80) vs 597 (115) ng/ml for PIO; 50 (16) vs 69 (78) ng.h/ml and 21 (5) vs 48 (32) ng/ml for REP; 92931 (44533) vs 58089 (23046) ng.h/ml and 6158 (1855) vs 4072 (1168) ng/ml for EFV. The geometric mean ratios with 90% confidence interval (GMR, 90% CI) of PIO or REP with and without EFV are presented in the table. An increase in PIO and REP dosage to 22.5 mg QD and 4 mg TID, respectively, was predicted to be sufficient to overcome EFV induction.

Drug	PK parameter	GMR	90% CI
Pioglitazone	AUC	0.53	0.46-0.60
	Cmax	0.77	0.73-0.80
Repaglinide	AUC	0.47	0.42-0.52
	Cmax	0.50	0.45-0.56

Conclusions: The prediction of DDI for drugs whose metabolism is concurrently induced and inhibited can be complex. The developed model, integrating both concurrent effects on CYPs and temporal changes in drug concentrations, shows that EFV has mainly an inducing effect on PIO and REP metabolism. PBPK modeling represents a useful tool to predict complex DDI as often encountered in multimorbid elderly HIV-infected patients and to support the design of prospective clinical trials.

532 In Silico Simulation of Interaction Between Rifampicin and Boosted Darunavir

Marco Siccardi; Owain Roberts; Rajith Rajoli; Laura Dickinson; Saye Khoo; Andrew Owen; David Back

University of Liverpool, Liverpool, United Kingdom

Background: The optimization of antiretroviral regimens in HIV-infected patients co-administered with anti-TB drugs is challenging since rifampicin (RIF), a principal element of the anti-TB therapy, is a strong inducer of key metabolic enzymes. Physiologically-based pharmacokinetic (PBPK) modelling represents an innovative approach to simulate clinical scenarios in the absence of clinical data, by integrating *in vitro* data in mathematical models. The aim of this research was to develop a PBPK model for the co-administration of ritonavir-boosted darunavir (DRV/r) and RIF and predict optimal dosing strategies to overcome the drug-drug interaction (DDI).

Methods: *In vitro* data describing physicochemical properties, absorption, distribution, metabolism and elimination (ADME) of DRV, ritonavir (RTV) and RIF, as well as the inhibition and induction potential of RTV and RIF were determined experimentally or obtained from the literature. A PBPK model was developed integrating experimental *in vitro* data in algorithms representing molecular, physiological and anatomical processes defining ADME. The PK of DRV/r and RIF was simulated in 100 virtual individuals. The impact of RIF (600mg *qd*) on DRV/r was determined and DRV and RTV *qd* and *bid* dose adjustments were simulated.

Results: Simulated DRV/r pharmacokinetic parameters were (mean ± SD) C_{trough} (2.02 ± 1.17 μg/ml), C_{max} (8.23 ± 1.73 μg/ml) and AUC (115.6 ± 32.9 μg/mL.h), which is in agreement with observed PK data for DRV/r 800/100 mg qd in HIV-infected patients: C_{trough} (2.11 ± 1.22 μg/ml), C_{max} (6.75 ± 1.68 μg/ml) and AUC (75.62 ± 26.44 μg/mL.h). The simulated effect of RIF on DRV exposure resulted in a decrement of 57.7% for AUC, 79.5% for C_{trough} and 34.6% for C_{max}. The effect of RIF was overcome by increasing the DRV/ r dose to 1600/200 mg *qd* or 800/100 mg *bid* (Table 1).

Table 1 Ritonavir-Boosted DRV dose adjustments (+RIF) and simulated effect on (mean ± SD) AUC_{24hr} compared to reference dosing (800/100 *qd* - RIF)

qd regimen + RIF	% of AUC_{24hr} compared to reference dosing (800/100 *qd* - RIF)	*bid* regimen + RIF	% of AUC_{24hr} compared to reference dosing (800/100 *qd* - RIF)
800/100	42 ± 18	600/100	89 ± 32
800/150	51 ± 21	600/150	93 ± 33
800/200	58 ± 26	600/200	98 ± 35
1200/100	66 ± 29	**800/100**	**118 ± 43**
1200/150	77 ± 30	**800/150**	**127 ± 44**
1200/200	83 ± 31	**800/200**	**142 ± 58**
1600/100	89 ± 43	**1200/100**	**171 ± 80**
1600/150	99 ± 53	**1200/150**	**186 ± 93**
1600/200	**111 ± 54**	**1200/200**	**197 ± 101**

Conclusions: The developed PBPK model predicted the in vivo pharmacokinetics of DRV/r and the interaction with RIF. Based on these findings, a DRV/r regimen of 1600/200 mg *qd* or 800/100 mg *bid* could mitigate the effect of RIF on DRV/r PK. Mechanistic evaluation of ADME can inform PBPK models and prediction of interaction between drugs. PBPK may be particularly helpful for the rational design of clinical trials evaluating dose adjustment strategies to overcome DDIs in patients concomitantly receiving antiretrovirals and anti-TB drugs.

533 Pharmacogenetics of Pregnancy-Induced Changes in Efavirenz Pharmacokinetics

Adeniyi Olagunju[1]; Oluseye Bolaji[2]; Alieu Amara[1]; Laura Else[1]; Ogechi Okafor[3]; Ebunoluwa Adejuyigbe[2]; Oyigboja Johnson[4]; David Back[1]; Saye Khoo[1]; Andrew Owen[1]

[1]University of Liverpool, Liverpool, United Kingdom; [2]Obafemi Awolowo University, Ile-Ife, Nigeria; [3]Bishop Murray Medical Centre, Makurdi, Nigeria; [4]Catholic Caritas Foundation of Nigeria, Makurdi, Nigeria

Background: Physiological changes during pregnancy coupled with single nucleotide polymorphisms (SNPs) in drug disposition genes are known to alter the pharmacokinetics (PK) of many drugs. In the present study the magnitude of pregnancy-induced changes in efavirenz (EFV) PK in genetically-defined subgroups was investigated.

Methods: This was an observational study with an enrichment design conducted in two phases. In the preliminary phase, we explored associations between selected *CYP2B6*, *NR1I3*, *CYP2A6*, and *ABCB1* SNPs and mid-dose EFV concentrations in an unselected cohort of HIV positive women during pregnancy and postpartum. In the second phase, patients were stratified according to *CYP2B6* 516G>T (rs3745274). Accordingly, randomly selected patients in each genotype group were invited for the intensive PK phase; samples were collected at 0.5, 1, 2, 4, 8, 12 and 24 hours after an observed evening dose of EFV.

Results: A total of 211 HIV positive women taking EFV-based regimens for prevention of mother-to-child transmission (PMTCT) of HIV during pregnancy (n = 77) or postpartum (n = 134) were recruited. Of the nine SNPs investigated, only *CYP2B6* 516G>T was independently associated with EFV plasma concentrations during both pregnancy and postpartum and was used to pre-select patients for the intensive PK phase. A global comparison showed a 42.6% increase in CL/F ($p = 0.02$), 29.8% reduction in AUC_{0-24} ($p = 0.02$) and 50.7% reduction in C_{min} ($p = 0.01$) during pregnancy compared with postpartum. The median (range) C_{min} was 1000 ng/ml (429-5190) and the change in C_{max} was not statistically significant ($p = 0.07$). However, when stratified for *CYP2B6* 516G>T status, EFV CL/F increased by 100% during pregnancy compared with postpartum ($p = 0.001$) in patients with the *CYP2B6* 516GG genotype. The AUC_{0-24}, C_{max} and C_{min} were reduced by 50.6% ($p = 0.001$), 17.2% ($p = 0.14$) and 61.6% ($p = 0.003$) during pregnancy, with values of 25,900 ng.hr/ml (21,700-32,600), 2640 ng/ml (1260-3490) and 592 ng/ml (429-917), respectively (Table 1).

Table 1. EFV pharmacokinetic parameters* during pregnancy and postpartum based on *CYP2B6<i/> 516G>T genotypes.*

	Clearance/F (L/hr)	AUC_{0-24} (ng.hr/ml)	C_{max} (ng/ml)	C_{min} (ng/ml)
All (CYP2B6 516GG, GT and TT)				
Pregnancy (n = 25)	14.1 (2.96-27.7)	42,600 (21,700-203,000)	3490 (1260-14400)	1000 (429-5190)
Postpartum (n = 19)	9.89 (3.39-20.7)	60,700 (29,000-177,000)	4850 (2050-9760)	2030 (755-6740)
Pregnancy vs Postpartum: % change	42.6	-29.8	-28.0	-50.7
p value	0.023	0.023	0.072	0.012
CYP2B6 516GG				
Pregnancy (n = 8)	23.2 (18.4-27.7)	25,900 (21,700-32,600)	2640 (1260-3490)	592 (429-917)
Postpartum (n = 6)	11.6 (9.37-18.4)	52,400 (32,600-64,000)	3190 (2700-3800)	1540 (867-2310)
Pregnancy vs Postpartum: % change	100	-50.6	-17.2	-61.6
p value	0.0013	0.0013	0.14	0.0027
CYP2B6 516GT				
Pregnancy (n = 14)	13.7 (2.96-23.3)	43,900 (25,700-203,000)	3660 (2490-14400)	1120 (571-5190)
Postpartum (n = 7)	11.9 (4.71-20.67)	50,700 (29,000-128,000)	4850 (2050-6780)	1520 (755-4860)
Pregnancy vs Postpartum: % change	15.1	-13.4	-24.5	-26.3
p value	0.85	0.85	0.43	0.63
CYP2B6 516TT				
Pregnancy (n = 3)	6.83 (5.22-8.15)	87,900 (73,700-115,000)	5770 (5320-5950)	2890 (2660-4030)
Postpartum (n = 6)	4.69 (3.39-5.35)	129,000 (112,000-177,000)	6940 (6370-9760)	5130 (3830-6740)
Pregnancy vs Postpartum: % change	45.6	-31.9	-16.9	-43.7
p value	0.095	0.095	0.024	0.048

*Values are presented as median (range) and *p<i/> values are for Mann-Whitney U test.*

Conclusions: The clinical relevance of these findings is uncertain, since dose-reduction of EFV in non-pregnant adults was previously not associated with increased risk of virological failure. Nevertheless, the impact of pharmacogenetic variability on mother-to-child transmission of HIV should be further studied.

534 Antiretroviral Drug Transporters and Metabolic Enzymes in Human Testicular Tissue

Billy Huang[1]; Md. Tozammel Hoque[1]; Mohammad-Ali Jenabian[3]; Kishanda Vyboh[2]; Nancy Sheehan[2]; Pierre Brassard[4]; Maud Bélanger[4]; Nicolas Chomont[5]; Jean-Pierre Routy[2]; Reina Bendayan[1]

[1]University of Toronto, Toronto, Canada; [2]McGill University, Montréal, Canada; [3]Université du Québec à Montréal, Montréal, Canada; [4]Metropolitan Centre of Plastic Surgery, Montréal, Canada; [5]Vaccine and Gene Therapy Institute of Florida, Port St Lucie, FL, US

Background: Previous studies have reported that HIV-1 is capable of both acute and persistent infection in the testes. The naturally restrictive environment in the testes due in part to the blood-testes-barrier (BTB), suggests that this barrier could restrict antiretroviral (ARV) penetration into this tissue and contribute to the formation of a viral sanctuary. This study aims to characterize drug transporters and metabolic enzymes expression and localization in the testes of uninfected and HIV-1-infected men receiving antiretroviral therapy (ART) in order to gain further insight on the factors regulating ARV disposition in this organ.

Methods: Testicular tissues were collected from uninfected men (N=8) and HIV-1 infected men on ART (plasma viral load <50 copies/mL for at least 6 months prior to surgery, N=5) who underwent elective orchiectomy for gender reassignment surgery at the Metropolitan Centre of Plastic Surgery in Montreal. We selected four ATP-binding cassette (ABC) transporters, six solute-carrier (SLC) transporters and two cytochrome P450 (CYP450) drug metabolic enzymes to study based on their relevance to ARV disposition, and assessed their gene and protein expression as well as tissue localization.

Results: In testicular tissues, we found that MRP2 and OATP2B1 were highly expressed at the mRNA level, BCRP showed moderate expression, while expression of P-gp, MRP1, OATP1A2, OATP1B1, OAT1, OCT1, CNT1, ENT2, CYP2D6 and CYP3A4 were low. However, we were able to detect robust protein expression for all transporters and metabolic enzymes analysed with the exception of OATP1A2 and OCT1. Overall, gene and protein expression did not differ significantly between the uninfected and ART-treated HIV-1-infected men. Our fluorescence microscopy results also indicate that transporters and metabolic enzymes are not limited to BTB localization but can be found throughout the testicular tissue.

Conclusions: It has been well documented that drug transporters and metabolic enzymes are capable of interacting with many commonly used ARVs, and could significantly affect drug disposition into tissues, especially at key blood-tissue barriers such as the blood-brain barrier. Our data are the first to demonstrate protein expression and localization of key drug transporters and metabolic enzymes in the testes of ART-treated HIV-1 infected men. Their presence suggests the testes are a complex pharmacological compartment that could limit the penetration of several ARVs in this tissue. *(Supported by CIHR and OGS)*

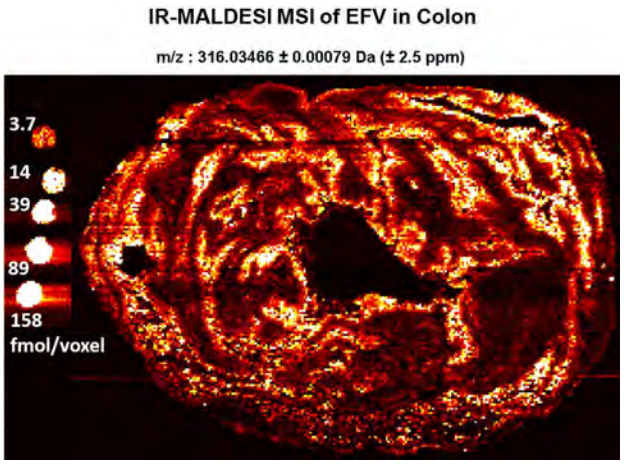
535 Imaging the Spatial Distribution of Efavirenz in Intact HIV Tissue Reservoirs

Elias P. Rosen[1]; Corbin G. Thompson[2]; Mark T. Bokhart[1]; Craig Sykes[2]; Yuri Fedoriw[2]; Paul Luciw[3]; David C. Muddiman[1]; Angela D.M. Kashuba[2]
[1]North Carolina State University, Raleigh, NC, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]University of California Davis, Davis, CA, US

Background: Methods to accurately evaluate ARV biodistribution within tissues are needed to design effective HIV therapy and eradication strategies. Here, we characterize the spatial distribution of efavirenz (EFV) within suspected reservoir tissues of a primate model using a novel approach to mass spectrometry imaging (MSI).

Methods: Reservoir tissues (GALT, lymph nodes, brain, testes) were removed at necropsy from an uninfected rhesus macaque dosed orally to steady-state with EFV. 10 μm cryosections of snap frozen tissue were discretized into 10^{-4} mm^3 voxels, resolving 100 μm features, and analyzed using an infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) source coupled to a Thermo Q-Exactive mass spectrometer. Response was calibrated by EFV standards on blank tissue, with a limit of detection of 180 attomole/voxel (57 fg/mm^3 tissue). The results were visualized using custom analysis software. Serial sections of tissue were utilized to validate MSI results by LC-MS, and stained to correlate observed EFV response with tissue morphology (H&E) and immunohistochemistry (CD3 staining).

Results: The presence of EFV was confirmed in all reservoir tissues by MSI, with varying total EFV penetration observed between tissue types. Mapping of EFV response indicated heterogeneous drug exposure. EFV concentration was substantially increased within the mucosa and lamina propria of the colorectal epithelium, specifically corresponding to high density of CD3+ T cells. No such mucosal enhancement was observed in the ileum. Lymph nodes showed focally increased signal in association with some, but not all, primary follicles. Within the brain, grey matter had enhanced EFV exposure relative to white matter. EFV concentration was lowest (167 pg/g tissue) in the basal ganglia, increasing to approximately two-fold in most other tissues (cerebrum, lymph nodes, spleen, testes, and most GALT), and highest in rectal tissue (3.6 fold).



Conclusions: This study is the first to map the biodistribution of an ARV in viral reservoir tissues. Differences in mucosal enhancement in the gut suggest potential differences in biologic transporter activity. Heterogeneous lymph node distribution may indicate insufficient exposure at important sites of viral replication. By differentiating and quantifying drug exposure between cell types within tissue, IR-MALDESI MSI offers a new capability to evaluate drug efficacy and will help inform the selection of optimal interventions to target active viral reservoirs.

WEDNESDAY, FEBRUARY 25, 2015

Session P-I1 Poster Session **Poster Hall**
2:30 pm – 4:00 pm

Drug Development

536 Inhibition of HIV-1 Replication by a Novel Acylguanidine-Based Molecule

Philip Mwimanzi[1]; Ian Tietjen[2]; Aniqa Shahid[1]; Scott C. Miller[2]; David Fedida[2]; Zabrina L. Brumme[1]; Mark Brockman[1]
[1]Simon Fraser University, Burnaby, Canada; [2]University of British Columbia, Vancouver, Canada

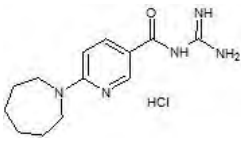
Background: Despite major successes in antiretroviral therapies against HIV-1, discovery of new drugs is necessary to enhance treatment options and counter resistance. BIT225 is an acylguanidine based compound that is reported to inhibit HIV-1 replication in myeloid cells by blocking the viroporin function of Vpu. Here, we test the anti-HIV-1 activity of a novel acylguanidine compound SM111.

Methods: We used a GFP-reporter T cell assay to test the ability of SM111 to inhibit replication of WT NL4.3, NL4.3ΔVpu (lacking *vpu*), and recombinant NL4.3 strains encoding major resistance mutations in *pol* for inhibitors of Reverse Transcriptase (RTI), Protease (PI) and Integrase (INI). Viral spread was monitored by flow cytometry over a 7-day period.

Cytotoxicity was evaluated using ViaCount (Millipore). WT NL4.3 was also passaged in the presence of SM111. Three independent drug-resistant strains were isolated, sequenced and assessed for their sensitivity to SM111. Vpu-mediated downregulation of CD4 and tetherin was monitored by flow cytometry.

Results: SM111 inhibited NL4.3 in a dose-dependent manner between 10μM and 100μM, and was non-toxic at 100μM concentration (viability >90%, similar to media control). Infected cells (%GFP+) were reduced >98% at 100μM (56.7% [55.3-57.7] in absence vs. 0.89 % [0.76-0.99] in presence of SM111) at day 7. Similar activity was observed against RTI, PI and INI resistance strains (>95% reduction in all cases). All SM111-resistant viruses encoded mutations in the transmembrane of Vpu, including a 5AA deletion (clone A), a stop codon at highly conserved W22 (clone C) or a substitution (I17R) (clone H), which impaired Vpu-mediated downregulation of CD4 and Tetherin. Notably, SM111 was only partially active against NL4.3ΔVpu (46.5% [44-48.2] in absence vs. 22.4% [20.1-25.7] in presence of drug); and growth of resistant strains was inhibited to various degrees by SM111 (92%; 54%; and 16% reduction for clone A; C; and H respectively).

Funded by CIHR & the Michael Smith Foundation for Health Research



SM111 chemical structure

Conclusions: SM111 is a novel compound that inhibits replication of WT as well as RTI, PI and INI resistant HIV-1 strains. Passaging of NL4.3 with SM111 selected major mutations in Vpu. However, these mutants and a ΔVpu strain remained partially sensitive to the drug, suggesting that Vpu may not be SM111's primary target. Our results indicate that SM111's mechanism of action is unique from current antiretroviral drugs, but more studies are necessary to explore this promising prototype.

537 4′-Ethynyl-2-Fluoro-2′-Deoxyadenosine (EFdA) Has an Extremely High Genetic Barrier, Persistently Exerting Highly Potent Activity Against a Variety of HIV-1 Isolates Including EFdA-Selected HIV-1 Variants

Kenji Maeda[1]; Yuki Takamatsu[1]; Satoru Kohgo[2]; Nicole S. Delino[1]; Simon B. Chang[1]; Kazuhiro Haraguchi[3]; Hiroaki Mitsuya[1]

[1]*National Institutes of Health (NIH), Bethesda, MD, US;* [2]*National Center for Global Health and Medicine, Tokyo, Japan;* [3]*Nihon Pharmaceutical University, Saitama, Japan*

Background: 4′-Ethynyl-2-fluoro-2′-deoxyadenosine (EFdA), a nucleoside reverse transcriptase inhibitor (NRTI), exerts potent activity against a wide spectrum of HIV-1 variants, including multi-drug-resistant HIV-1 isolates. EFdA is currently under clinical trials in the US as a peroral QD-possible therapeutic against HIV-1 infection and AIDS. We have recently selected *in vitro* HIV-1 variants resistant against EFdA (HIV-1^{EFdA-R}), carrying M41L/D67D/T69G/K70R/L74I/V75T/M184V/T215F/K219Q substitutions in reverse transcriptase (Maeda K *et al. Antiviral Therapy* 19:179-189, 2014). In the present study, we newly designed and synthesized a variety of novel 4′-modified NRTIs, which exert activity against various multi-drug-resistant-HIV-1 variants including HIV-1^{EFdA-R}.

Methods: Anti-HIV-1 activity of EFdA and various newly synthesized EFdA-related NRTIs were examined using various cell-based assays including the MTT assay and p24 assay. Cytotoxicity of such NRTIs was also determined.

Results: Multiple EFdA-related NRTIs were identified to be active against wild-type HIV-1 (HIV-1^{WT}) with IC_{50} values of 2 - 207 nM, most of which were also active against viruses carrying conventional multi-NRTI-resistance-associated amino acid substitutions such as K65R, K70R, and M184V (HIV-1^{MDR}s) with IC_{50} values of 3 - 404 nM. However, most of such 4′-modified NRTIs failed to be active against HIV-1^{EFdA-R} (>1,000 nM): only two 4′-modified-pyrimidine-based NRTIs, YMS-99066 and YMS-03072, were identified to be active against HIV-1^{EFdA-R} with IC_{50} values of 91 and 131 nM, respectively. Against HIV-1^{WT} and HIV-1^{MDR}s, EFdA exerted the most potent activity with IC_{50} values of 0.1 - 2 nM. Against HIV-1^{EFdA-R}, EFdA also exerted the most potent activity with IC_{50} value of 44 nM. The CC_{50} value of EFdA was 19.2 μM with a selectivity index of 64,000.

Conclusions: We newly synthesized various 4′-modified NRTIs and tested their activity against HIV-1^{WT}, HIV-1^{MDR}s, and HIV-1^{EFdA-R}. The present data demonstrate that among a variety of 4′-modified purine- and pyrimidine-based NRTIs, EFdA persistently exerts the most potent activity against even EFdA-selected HIV-1^{EFdA-R} and warrant further clinical development as a novel QD-possible NRTI with an extremely high genetic barrier and potency against a variety of multi-drug-resistant HIV-1 variants.

538 GSK2838232, a Second Generation HIV-1 Maturation Inhibitor With an Optimized Virology Profile

Jerry Jeffrey[1]; Ping Wang[1]; Charlene McDanal[1]; Pauline J. Shipper[2]; Kevin Brown[1]; Cristin Galardi[1]; Jun Tang[1]; Monique Nijhuis[2]; Brian Johns[1]

[1]*GlaxoSmithKline, Research Triangle Park, NC, US;* [2]*University of Utrecht, Utrecht, Netherlands*

Background: The first generation HIV-1 maturation inhibitor bevirimat demonstrated clinical efficacy in infected subjects. However, gag polymorphisms in both capsid (p24) and Sp1 regions were liabilities for bevirimat potency against a broad range of HIV-1 isolates; therefore limiting the clinical utility of bevirimat to 40% of HIV patients without polymorphisms in the 369-370 region of gag.

Methods: We aimed to improve the virology profile of an HIV-1 maturation inhibitor by combining a medicinal chemistry approach with a virology triage strategy focused on activity against gag polymorphisms. Initial anti-viral activity was assessed in an MT4 assay using NL4-3 with a consensus clade B capsid/Sp1 region and compared to a V370A mutant. Compounds with no loss of potency against V370A were progressed into mechanism of action studies and a panel of HIV-1 isolates in a PBMC anti-viral assay.

Results: GSK2838232 was identified using this strategy with an NL4-3 IC_{50} at 0.81nM and a similar IC_{50} against V370A at 0.71nM. The effect of human serum addition was assessed on GSK2838232 potency and showed no effect with increasing serum concentrations up to 40%. When tested in a panel of 26 HIV-1 isolates covering a diversity of capsid/Sp1 genotypes in clades A, AE, B, and C using a PBMC based assay, GSK2838232 had a mean IC_{50} of 1.6nM (IC_{50} range 0.8nM to 4.3nM). The broad spectrum isolate coverage was confirmed by an external contract research group in a panel of 60 isolates covering various clades with only 1 isolate (92BR014) not inhibited by GSK2838232. The external panel also included viruses with known resistance genotypes to show that GSK2838232 is not cross resistant with marketed anti-retroviral products. Based on previous observations of bevirimat potency and HIV protease inhibitor (PI) treatment, GSK2838232 was tested against a panel of viruses isolated from subjects prior to and post PI treatment and did not have a correlation in potency depending on PI experience.

Conclusions: These data demonstrate the optimized anti-viral properties of GSK2838232 and support the further assessment of this compound as a second generation maturation inhibitor for the treatment HIV-1 infected subjects.

539 Maturation Inhibitor Mechanistic Studies - Differential Inhibition of Gag Polymorphs

Zeyu Lin[1]; Joseph Cantone[1]; Tricia Protack[1]; Dieter Drexler[1]; Beata Nowicka-Sans[1]; Yuan Tian[3]; Zheng Liu[1]; Mark Krystal[1]; Alicia Regueiro-Ren[1]; **Ira B. Dicker**[1]

[1]Bristol-Myers Squibb Co, Wallingford, CT, US; [2]Bristol-Myers Squibb Co, Wallingford, CT, US; [3]Bristol-Myers Squibb Co, Princeton, NJ, US; [4]Bristol-Myers Squibb Co, Wallingford, CT, US

Background: HIV-1 maturation inhibitors (MIs) are a class of inhibitors that may be effective in the treatment of HIV-1. MIs disrupt the final step in the HIV-1 protease-mediated cleavage of the HIV-1 Gag polyprotein, between capsid (CA) and spacer peptide 1 (SP1), which is responsible for a major conformational rearrangement of viral proteins within the virion, leading to the production of infectious virus. An MI, bevirimat, previously terminated from development as a result of inadequate coverage of polymorphic Gag variants present in the general HIV-1 population, was used as a model compound. Understanding the mechanism of action of MIs in greater detail may be of value to help guide the development of MIs with improved genotypic coverage.

Methods: In this study, we developed a novel LC/MS assay using assembled Gag virus-like particles (VLPs) to quantitatively characterize the kinetics of CA/SP1 cleavage of a family of Gag variant genotypes. These variant VLPs contained site-directed mutations that alter susceptibility of HIV-1 to bevirimat. This method was also used to study inhibition by bevirimat and a second MI in this system. Secondarily, we used a radioligand binding assay to measure the kinetics of dissociation of bevirimat and this second MI to the same Gag variant VLPs.

Results: The LC/MS cleavage assay allows for the simultaneous quantization of both cleavage steps leading to the production of free SP1 (SP1/nucleocapsid and CA/SP1) while monitoring the effects of MIs on these processes. The innate rates of cleavage at CA/SP1 roughly correlate inversely with the ability of bevirimat to inhibit these HIV-1 polymorphic viruses in antiviral assays; genotypes with more rapid CA/SP1 cleavage profiles are less sensitive to bevirimat. The MI kinetic dissociation data indicate that improvements to polymorphic antiviral activity arise from increases in MI dissociation half-lives toward those polymorphs.

Conclusions: Together, the innate polymorph cleavage rates at CA/SP1 and the MI-specific kinetic dissociation data suggest a model for MI inhibition of HIV-1 protease mediated CA/SP1 cleavage that can be used to quantify MI antiviral behavior as a function of both MI and Gag polymorphs.

540 Late-Stage Integrase-LEDGF Inhibitors Mode of Action and Acquisition of Resistance

Richard Benarous[1]; Erwann Le Rouzic[1]; Nikki van Bel[2]; Yme Van der Velden[2]; Damien Bonnard[1]; Atze Das[2]; Celine Amadori[1]; Alessia Zamborlini[4]; Stephane Emiliani[3]; Ben Berkhout[2]

[1]Biodim Mutabilis, Romainville, France; [2]Academic Medical centre, Amsterdam, Netherlands; [3]Inserm CNRS, Paris, France; [4]U944 UMR7212, Inserm CNRS, Paris, France

Background: We and others described a new class of HIV-1 integrase (IN) allosteric inhibitors that bind to the LEDGF binding pocket of IN and inhibit IN-LEDGF interaction. Mutabilis developed very active compounds of this class. Designed to interfere with IN-LEDGF interaction during integration, the major impact of these inhibitors was found on virus maturation, causing a reverse transcription defect in target cells independent of LEDGF and linked to compound-induced IN oligomerization. We wanted to determine whether viral RNA packaging was affected and study IN mutants resistant to these inhibitors and interaction of IN with other cofactors such as Transportin (TNPO3) and VHL-binding protein 1 (VBP1).

Methods: Virus RNA was isolated, submitted to northern blot and t-RNA primer extension, interaction of IN with cofactors, or IN oligomerization, were studied by HTRF. Resistance mutations were identified by serial passages with increasing concentration of inhibitors during NL4-3 infection of MT4 cells.

Results: Wild-type level of HIV-1 genomic RNA was packaged in defective virions in dimeric state, tRNAlys3 primer for reverse transcription was properly placed and could be extended. Reverse transcriptase from defective virions was fully active. Several mutations in IN resulted in variable resistance to this class of inhibitors. The most detrimental mutation was T174I with fold change (FC) in EC50 antiretroviral activity over 200. Other mutations were selected, A128T and N222K were the most frequent ones, with much lower FC values around 4-5. These mutants were impaired for interaction with LEDGF to various extents but conserved wt strand transfer activity and IN-IN subunit interaction.. Ternary complexes could be formed between IN LEDGF and TNPO3, and between IN VBP1 and TNPO3. IN was the link between LEDGF and TNPO3. In the IN-VBP1-TNPO3 complex, each protein could interact with its two other partners.

Conclusions: Inhibition of reverse transcription promoted by IN-LEDGF inhibitors in target cells likely reflects the mislocalization of the components in the aberrant virus particle. Most of the resistance mutations were in the LEDGF-binding pocket, affecting the affinity of the inhibitors for IN. N222K, in the C-ter domain of IN is a notable exception. The genetic barrier to resistance to this first generation of IN-LEDGF allosteric inhibitors is similar to that observed for Nevirapine. We are developing a second generation of inhibitors with improved resistance profile.

541 BMS-986001: A Promising Candidate for HIV-2 Treatment

Robert A. Smith[1]; Dana Raugi[1]; Kate Parker[1]; Mariah Oakes[1]; Papa Salif Sow[2]; Selly Ba[2]; Moussa Seydi[2]; Geoffrey S. Gottlieb[1]
On behalf of the University of Washington-Dakar HIV-2 Study Group

[1]University of Washington, Seattle, WA, US; [2]CHNU de Fann, Dakar, Senegal

Background: New antiretrovirals (ARV) are urgently needed for the treatment of HIV-2 infection. BMS-986001 is an investigational NRTI that potently suppresses HIV-1 replication in culture and maintains full or partial activity against NRTI-resistant HIV-1 mutants. To examine the potential utility of the drug in HIV-2–infected individuals, we compared the susceptibilities of wild-type HIV-1 and HIV-2 isolates to BMS-986001 in culture and assessed its activity against HIV-2 variants containing clinically-relevant drug resistance mutations in RT.

Methods: Wild-type HIV-1 and HIV-2 strains were obtained from the NIH AIDS Reagent Program. Site-directed mutants of HIV-2 and a full-length recombinant clone containing the RT sequence from an ARV-experienced HIV-2 patient (encoding K65R, N69S, V111I, Q151M and M184V) were constructed in the HIV-2 pROD9 background. HeLa-CD4–based indicator cells (MAGIC-5A) were used to quantify drug sensitivity in a single cycle of viral replication.

Results: BMS-986001 inhibited HIV-1 isolates NL4-3 (group M/subtype B), LAI (M/B), 92UG029 (M/A) and MVP5180-91 (group O) with EC_{50} values ranging from 0.47 to 0.91 μM (mean ± SD = 0.62 ± 0.21 μM). Similar EC_{50} values were observed for the parental compound stavudine (d4T) against NL4-3 and ROD9 (1.32 ± 0.33 and 1.29 ± 0.47 μM, respectively). In contrast, all seven of the group A HIV-2 isolates tested in our assays were more sensitive to BMS-986001, with EC_{50}s ~10-fold lower than that of HIV-1 (mean = 0.065 ± 0.091 μM, range = 0.030 to 0.081 μM; p = 0.004, Mann-Whitney test). Increased BMS-986001 sensitivity was also observed for a prototypic HIV-2 group B strain (EHO; EC_{50} = 0.042 ± 0.009 μM). HIV-2_{ROD9} RT mutants K65R and Q151M were equal to or slightly more sensitive to the drug than wild-type HIV-2_{ROD9}, and mutants M184V and K65R+M184V showed sensitivities comparable to wild-type HIV-1_{NL4-3}. Higher levels of BMS-986001 resistance (>30-fold) were observed for HIV-2 mutants Q151M+M184V, K65R+Q151M+M184V, and the patient-derived RT clone.

Conclusions: BMS-986001 inhibits wild-type HIV-2 replication with EC_{50}s in the nanomolar range and retains substantial activity against NRTI-resistant HIV-2 mutants. To our knowledge, this is the first and only report of an antiretroviral compound that, when tested against a diverse panel of HIV-1 and HIV-2 isolates, exhibits more potent activity against HIV-2 than HIV-1.

542 Dual Loaded Sustained Release Core-Shell Nanoparticles for Anti-HIV Therapy

Hilliard L. Kutscher[1]; Jessica L. Reynolds[1]; Faithful Makita[2]; Sara DiTursi[1]; Jacob Milling[1]; Jesse Hanchett[1]; Charles C. Maponga[2]; Paras N. Prasad[1]; Gene D. Morse[1]
[1]University at Buffalo, Buffalo, NY, US; [2]University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe

Background: Human immunodeficiency virus (HIV) is the world's deadliest infectious disease and progressively suppresses the immune system leading to mortality. Due to length of treatment, high pill burden and adverse effects, patient non-adherence often occurs resulting in viral resistance to current therapeutic regimens. Biodegradable poly(lactic-co-glycolic acid (PLGA) nanoparticles (NPs) are able to control the release of lamivudine and nevirapine, two current front-line therapeutic agents in Africa, and enhance cellular uptake in macrophages, a viral reservoir using a surface modifying sugar (chitosan). Common methods of NP fabrication predominantly result in NP sizes >200nm, however to utilize a hollow-fiber pharmacokinetic model to better optimize drug therapies, the size must be <200nm. Furthermore, a decreased size may also improve NP penetration to the brain, and decrease reticuloendothelial system (RES) capture.

Methods: Core-shell chitosan-PLGA NPs were fabricated using a water-oil-water double emulsion (w/o/w) method, followed by solvent evaporation to encapsulate anti-retroviral drug(s). NPs were characterized for size and polydispersity using dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA); surface charge using a zeta potential analyzer; surface morphology using transmission electron microscopy (TEM); and drug encapsulation, dissolution and intracellular concentration using high performance liquid chromatography (HPLC). Monocyte derived macrophages (MDMs) were cultured using standard approaches.

Results: Core-shell NPs display a capsule-like morphology indicating a core-shell structure; a positive zeta potential when chitosan was incorporated during fabrication further confirming the core-shell structure; a decreased size (<150nm); and a sustained release over 24 hours. Intracellular drug concentrations in MDMs were higher in NP-drug formulations compared to free drug samples.

Conclusions: In summary, we demonstrate that chitosan-PLGA NPs are capable of 1) being made to smaller dimensions using commonly available methods in the lab and 2) can encapsulate both lamivudine and nevirapine. These positively charged core-shell nanoparticles deliver therapeutics to viral reservoirs and are a revolutionary approach for a more effective, efficient and affordable treatment.

543 Chemical Facilitated Endosomal Storage of Long-Acting Antiretroviral Nanoparticles

Dongwei Guo; **Prasanta K. Dash**; Gang Zhang; Mariluz Arainga; Jaclyn Knibbe; JoEllyn McMillan; Larisa Poluektova; Harris Gelbard; Santhi Gorantla; Howard Gendelman
University of Nebraska Medical Center, Omaha, NE, US

Background: Suboptimal adherence to antiretroviral therapy (ART) for HIV-1 begets viral mutations and drug resistance. This might be reduced or eliminated by maintenance of plasma and tissue drug levels above an effective dose for prolonged time periods after single dose administration. To achieve this, we sought pharmacologic approaches that would augment ART depots in intracellular organelles free from pathways operative for drug elimination.

Methods: A mixed lineage kinase-3 inhibitor URMC-099, developed in our laboratories, was investigated for its abilities to affect ART storage and antiviral activities. Humanized HIV-1 infected NOD/SCID/IL2Rγc$^{-/-}$ (NSG) mice and monocyte-derived macrophages (MDM) were treated with or without nanoformulated ritonavir (RTV)-boosted atazanavir (nanoATV/r), co-administered with URMC-099. 22-weeks old humanized-NSG mice were infected with HIV-1$_{ADA}$, followed by administration of URMC-099 daily and nanoformulated ATV and RTV (nanoART) weekly for three weeks starting 10 weeks post-infection, when the mice were at the peak of their viral load (VL). Peripheral VL, ratio of CD4$^+$ and CD8$^+$ T-lymphocytes, drug level in plasma and organs and pathological changes in lymphoid and brain tissues were investigated.

Results: Co-administration of URMC-099 and nanoATV/r reduced viral load (VL) below detectable levels in plasma and reduced HIV-1p24+ lymphocyte numbers in spleen. We found very small amounts of residual HIV-1 found in infected humanized mice significantly below what was seen by nanoATV/r alone treatment. This effect on VL was associated with elevated nanoATV/r depots in macrophages and paralleled URMC-099 induction of ATV and RTV in spleen and liver. Proteomic and Western blot validation assays demonstrated that the antiretroviral effect was associated with accumulation of HIV-1 and nanoATV/r as well as reduced progeny virions in Rab 7- and 11-labeled recycling and late endosomes. URMC-099 induced dose-dependent reductions in HIV-1p24 and reverse transcriptase activity within Rab 5-, 7- and 11-labeled endosomes in infected human monocyte-derived macrophages but only when administered with nanoformulated drugs.

Conclusions: Combination URMC-099 and nanoATV/r treatments offers a unique means to increase antiretroviral efficacy by enhancing accumulation of drug particle depots at endosomal sites of progeny virion maturation.

TUESDAY, FEBRUARY 24, 2015

Session P-J1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

ART: Recent Perspectives

544 24-Weeks Virologic Efficacy of Fozivudine in ART-Naïve Patients From Africa

Arne Kroidl[1]; Tessa Lennemann[1]; Frederic Ello[2]; Jimson Mgaya[3]; Raoul Moh[2]; Lucas Maganga[3]; Serge P. Eholié[2]; Pierre-Marie Girard[4]; Friedrich von Massow[5]; Christine Danel[6]
[1]Medical Center of the University of Munich (LMU), Munich, Germany; [2]CHU de Treichville, Abidjan, Côte d'Ivoire; [3]NIMR–Mbeya Medical Research Center, Mbeya, United Republic of Tanzania; [4]University Hospital Saint-Antoine, Paris, France; [5]Institute for Life Sciences and Environment GmbH, Heidelberg, Germany; [6]Programme PAC-CI, ANRS, Abidjan, Côte d'Ivoire

Background: Zidovudine (ZDV) is a frequently used NRTI in resources constraint settings but limited by toxicity. Fozivudine (FZD) is a ZDV pro-drug with a linked lipid domain and is bio-activated intracellularly to ZVD-monophosphate by outer membrane enzymes NPP1/3 preferentially expressed on mononuclear cells but not on bone marrow cells. FZD promises improved myelotoxicity profiles and once daily dosing.

Methods: FATI-1 was a multicentre, randomized, open label phase II proof of concept and dose finding trial investigating three different FZD doses (800mg QD, 600mg BID, 1200mg QD) versus ZDV (300mg BID) plus 3TC and EFV in HIV infected, ART naïve patients from Tanzania and Côte d'Ivoire. The primary objective was to demonstrate virological efficacy after 24 weeks, secondary endpoints included toxicity and pharmacokinetic outcome. Endpoints were based on per protocol (PP) and intent-to treat (ITT) analysis, the latter including patients with treatment modifications due to toxicity or virologic failure only.

Results: Treatment started in 119 participants (78% females, mean age 38 years, CD4 238 cells/μl, HIV-RNA Log$_{10}$ 4.99); characteristics did not differ between arms. Overall 105 (88.2%) participants were included in the PP and 110 (92.4%) in the ITT analysis. Reasons for early treatment modification were severe rash (1), elevated liver enzymes (1), severe anemia (2) and virologic failure (1). Week 24 outcome showed HIV-RNA <50 copies/ml in PP 83.8% (ITT 80.0%), <400 copies/ml in PP 91.4% (ITT 87.3%) with a mean PP CD4 increase of 127 cells/μl. Outcome did not differ between study arms. Virologic failure >1000 copies/ml confirmed by two measurements was seen in 4 cases, no drug resistance

mutations were found in 2 and the K103N NNRTI mutation in 2 cases, one of those retrospectively identified as transmitted mutation at baseline. Neutropenia was overall frequently observed, toxicity grade increases by 3 or 4 grades compared to baseline were significantly more common in the ZDV compared to combined FZD arms (p=<0.001). Grade III/IV anemia was seen only in 2 cases (Arm B with sickle cell trait and arm D). Mean decrease of hemoglobin and neutrophils at early time points were more pronounced in the ZDV as compared to combined FZD arms (p=0.033 and 0.004 resp).

	Total N=119	Arm A FZD 600mg BID N=30	Arm B FZD 800mg QD N=29	Arm C FZD 1200mg QD N=29	Arm D ZDV 300mg BID N=31	p-value #
HIV-RNA <50 copies/ml, PP, N (%)	88/105 (83.8)	24/27 (88.9)	19/22 (86.4)	21/27 (77.8)	24/29 (82.8)	0.713
HIV-RNA <400 copies/ml, PP, N (%)	96/105 (91.4)	25/27 (92.6)	20/22 (90.9)	23/27 (85.2)	28/29 (96.6)	0.500
HIV-RNA <50 copies/ml, ITT, N (%)	88/110 (80.0)	24/27 (88.9)	19/24 (79.2)	21/28 (75.0)	24/31 (77.2)	0.591
HIV-RNA <400 copies/ml, ITT, N (%)	96/110 (87.3)	25/27 (92.6)	20/24 (83.3)	23/28 (82.1)	28/31 (90.3)	0.584
Virologic failure>1000 copies/ml, N (%)	4/110 (3.6)	0/27 (0)	1/24 (4.2)	1/28 (3.6)	2/31 (6.5)	-
Mean CD4 increase, Week 24 (cells/μL)	127	154	91	135	121	0.588
Mean Hb decrease, Week 4 (g/dL)	-0.59	-0.47			-0.92	**0.033**
Grade III/IV anemia, N (%)	2/118 (1.7)	1/87 (1.2)			1/31 (3.2)	-
Mean neutrophil decrease, Week 4 (x 10^3 cells/μL)	-0.416	-0.274			-0.794	**0.004**
Grade 3/4 decrease neutropenia, N (%)*	16/118 (13.6)	6/87 (6.9)			10/31 (32.3)	**<0.001**

*Grades do not represent absolute toxicity but subtracted grade increase from baseline toxicity grades (ANRS Toxicity Scale, Vers. 1.0, 4th Nov 2008).

p-values from Kruskal-Wallis and Fisher's exact tests.

Conclusions: Virologic 24 weeks efficacy was demonstrated in a FZD based ART regimen. Despite a small sample size evidence for reduced myelotoxicity in FZD compared to ZDV based regimens was seen. PK data for dose finding criteria is pending.

545 Attachment Inhibitor Prodrug BMS–663068 in ARV-Experienced Subjects: Week 48 Analysis

Melanie Thompson[1]; Jay Lalezari[2]; Richard Kaplan[3]; Yvette Pinedo[4]; Otto Sussman Pena[5]; Pedro Cahn[6]; David A. Stock[7]; Samit R. Joshi[7]; George J. Hanna[8]; Max Lataillade[7]

[1]AIDS Research Consortium of Atlanta, Atlanta, GA, US; [2]Quest Clinical Research, San Francisco, CA, US; [3]Desmond Tutu HIV Foundation, Cape Town, South Africa; [4]Asociacion Civil Via Libre, Lima, Peru; [5]Asistencia Cientifica de Alta Complejidad SAS, Bogotá, Colombia; [6]Fundacion Huesped, Buenos Aires, Argentina; [7]Bristol-Myers Squibb, Wallingford, CT, US; [8]Bristol-Myers Squibb, Princeton, NJ, US

Background: BMS-663068 is a prodrug of BMS-626529, a first-in-class attachment inhibitor that binds directly to HIV-1 gp120, preventing initial viral attachment and entry into host CD4+ T-cells. AI438011 is an ongoing Phase 2b, randomized, active-controlled trial investigating the safety, efficacy and dose–response of BMS-663068 vs atazanavir/ritonavir (ATV/r) in treatment-experienced (TE) HIV-1-infected patients (pts). At Week 24, BMS663068 arms had similar response rates to ATV/r and were generally well tolerated with no BMS-663068-related SAEs or AEs leading to discontinuation (D/C). Here we report the Week 48 results.

Methods: TE adults (≥1 week exposure to ≥1 ARV) with viral load (VL) ≥1,000 c/mL and susceptibility to all study drugs (including a conservative cut-off for BMS-626529 IC_{50} <100 nM) were randomized equally to four BMS-663068 groups (400 or 800 mg BID; 600 or 1200 mg QD) and a control group (ATV/r 300/100 mg QD), each with a background of raltegravir (RAL) 400 mg BID + tenofovir disoproxil fumarate (TDF) 300 mg QD. Efficacy and safety at Week 48 were assessed as secondary endpoints.

Results: 254 pts were randomized and 251 were treated across all arms. At baseline (BL), demographics were similar across arms: median age=39 yrs, male=60%, non-white=62%, median BL VL=4.85 $\log_{10}$ c/mL (43% had VL ≥100,000 c/mL), median CD4 count=230 cells/μL (38% had <200 CD4 cells/μL). Approximately 50% of pts had ≥1 major NRTI, NNRTI or PI resistance-associated mutation at BL. Through Week 48, 61–82% of BMS-663068 pts and 71% of ATV/r pts had HIV-1 RNA <50 c/mL (Table, mITT FDA Snapshot). Similarly, 77–95% of BMS-663068 pts and 88% of ATV/r pts had HIV-1 RNA <50 c/mL in the observed analysis (Table). Mean increase in CD4 counts from baseline were 141–199 cells/μL across BMS-663068 arms and 179 cells/μL for the ATV/r arm. Observed virologic response rates across the BMS-663068 and ATV/r arms by BL VL <100,000c/mL were 74–100% vs 96%, respectively and by BL VL ≥100,000c/mL were 60–91% vs 71%, respectively. All BMS-663068 doses were generally well tolerated and no BMS-663068-related AEs led to D/C.

Parameter	BMS-663068 + TDF (300 mg QD) + RAL (400 mg BID)				ATV/r (300/100 mg QD) + TDF (300 mg QD) + RAL (400 mg BID)
	400 mg BID	800 mg BID	600 mg QD	1200 mg QD	
Week 48 mITT (FDA SnapShot algorithm), N	50	49	51	50	51
HIV RNA <50 c/mL, n (%)	41 (82)	30 (61)	35 (69)	34 (68)	36 (71)
HIV RNA <400 c/mL, n (%)	43 (86)	37 (76)	43 (84)	40 (80)	38 (75)
Week 48 Observed (Subjects with data within Week 48 window), N	43	39	45	42	41
HIV RNA <50 c/mL, n (%)	41 (95)	30 (77)	35 (78)	34 (81)	36 (88)
HIV RNA <400 c/mL, n (%)	43 (100)	37 (95)	43 (96)	40 (95)	38 (93)

ATV/r, ritonavir-boosted atazanavir; mITT, modified intent - to - treat; TDF, tenofovir disoproxil fumarate; RAL, raltegravir

Week 48 Efficacy Results

Conclusions: Through Week 48, BMS-663068 continues to show similar efficacy to ATV/r in TE pts. Virologic response rates (mITT and observed) and immunologic reconstitution were similar across the BMS-663068 and ATV/r arms through Week 48. All BMS-663068 doses were generally well tolerated with no dose response safety signals reported. These results support the continued development of BMS-663068.

546 Delay in Antiretroviral Therapy Is Not Associated With Increased Virologic Failure

Ashita S. Batavia[1]; Patrice Severe[2]; Marc Antoine Jean Juste[2]; Rode Secours[2]; Daphne C. Bernard[2]; William J. Pape[2]; Daniel Fitzgerald[1]

[1]Weill Cornell Medical College, New York, NY, US; [2]GHESKIO Center, Port-au-Prince, Haiti

Background: Viral load is the most important marker of response to antiretroviral therapy (ART). Decreases in viral load following ART initiation are associated with decreases in mortality and HIV disease progression. Early ART initiation provides added mortality advantages, but it has not been clearly demonstrated whether this is related to differences in rates of virologic failure.

Methods: 816 HIV-infected treatment-naïve Haitian subjects with CD4 counts between 200-350 cells/mm^3 were randomized to early (within 2 weeks; N=408) versus delayed ART initiation (CD4 count ≤200 cells/mm^3 or development of an AIDS-defining condition; N=408) between 8/1/2005 and 7/31/2008. In the early arm, 340 subjects had viral load data available at 2 years. In the delayed arm, 23 subjects died and 30 were lost prior to ART initiation. Of the 355 subjects in the delayed arm that started therapy, 274 had viral load data available at 2 years. A validated 9-item food security questionnaire was administered at ART initiation, and all subjects were then scheduled for follow-up with a study physician at 1, 2, 3, 6, 12, 18 and 24 months; during these visits ART adherence was assessed using 3-day recall. All analyses were performed using stata 13 software (StataCorps, TX).

Results: At ART initiation, subjects in the delayed arm (N=355) had more advanced HIV disease (33.7% vs. 19.10% WHO Clinical Stage III/IV; p-value <0.001) and greater food insecurity (74.1% vs. 54.8% scoring 5-9; p-value <0.001). After 2 years on therapy there was no difference in virologic failure (viral load >50 copies/μL) between the arms (21.6% early vs. 22.3% delayed). Table 1 shows that in multivariate analysis the predictors of virologic failure were younger age (OR per additional year 0.98; 95%CI: 0.96-0.99, p-value 0.014), annual income less than US$100 (OR 1.56, 95%CI: 1.06-2.31, p-value 0.026), suboptimal adherence (OR 1.81, 95%CI: 1.25-2.63; p-value 0.002) and number of visits attended (OR 0.68, 95%CI: 0.57-0.82, p-value <0.001).

	Univariate	Multivariate Model 1	Multivariate Model 2
	Odds Ratio (95%CI, p-value)	Odds Ratio (95%CI, p-value)	Odds Ratio (95%CI, p-value)
Early ART initiation arm	0.89 (0.62-1.27; 0.515)	0.97 (0.66-1.41; 0.867)	*Excluded*
Age at ART initiation	0.97 (0.96-0.99; 0.008)	0.98 (0.96-0.99; 0.031)	0.98 (0.96-0.99; 0.014)
Female	1.14 (0.79-1.63; 0.48)	*Excluded*	*Excluded*
Marital status			
* Married	1 (reference)	1 (reference)	*Excluded*
* Unmarried/ widowed	1.79 (1.09-2.97; 0.022)	1.60 (0.95-2.70; 0.077)	*Excluded*
Food Security Score			
* 0 - 3	1 (reference)	*Excluded*	*Excluded*
* 4 - 6	1.46 (0.73-2.91; 0.283)	*Excluded*	*Excluded*
* 5 - 9	1.49 (0.97-2.29; 0.072)	*Excluded*	*Excluded*
Annual income <US$100	1.57 (1.07-2.29; 0.020)	1.55 (1.05-2.30; 0.029)	1.56 (1.06-2.31; 0.026)
Literate	0.88 (0.60-1.29; 0.508)	*Excluded*	*Excluded*
WHO Clinical stage at ART initiation			
* Stage I	1 (reference)	*Excluded*	*Excluded*
* Stage II	1.08 (0.70-1.65; 0.739)	*Excluded*	*Excluded*
* Stage III or IV	1.07 (0.65-1.76; 0.782)	*Excluded*	*Excluded*
Tuberculosis at ART initiation	2.25 (1.12-4.55; 0.023)	1.84 (0.87-3.90; 0.111)	*Excluded*
Suboptimal adherence	1.91 (1.33-2.74; <0.001)	1.79 (1.23-2.61; 0.002)	1.81 (1.25-2.63, 0.002)
Number of visits	0.77 (0.66-0.89; 0.001)	0.69 (0.57-0.84; <0.001)	0.68 (0.57-0.82; <0.001)

Predictors of Virologic Failure (Viral load > 50 copies/μL) at 2 years: Univariate and Multivariate Logistic Regression

Conclusions: Delaying ART initiation until CD4 count ≤200 cells/mm^3 or development of an AIDS defining condition resulted in significant pre-ART attrition, interim progression of HIV disease and greater food insecurity. Delayed ART initiation was not associated with increased virologic failure. Predictors of virologic failure were related to age, income and adherence to therapy.

547 Effects of Quadruple First-Line ART on Mucosal Immunity

Sergio Serrano-Villar[1]; Talía Sainz[2]; Surinder Mann[3]; Zhong-Min Ma[3]; Christopher Miller[3]; Netanya S. Utay[4]; Basile Siewe[5]; Tae Wook-Chun[6]; Paolo Troia-Cancio[3]; David Asmuth[3]

[1]University Hospital Ramón y Cajal, Madrid, Spain; [2]University Hospital Gregorio Marañón, Madrid, Spain; [3]University of California Davis, Sacramento, CA, US; [4]University of Texas, Galveston, TX, US; [5]Rush University Medical Center, Chicago, IL, US; [6]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

Background: HIV infection depletes gut mucosa, which leads to bacterial translocation and T-cell dysfunction. Despite effective ART, CD4+ T-cell depletion and HIV replication persist in the gut. We evaluated the impact of quadruple ART on systemic/mucosal immunity and bacterial translocation.

Methods: 33 ART-naïve HIV patients (pts) were randomized to efavirenz (EFV), maraviroc (MRV) or MRV + raltegravir (MRV+RAL), each with TDF/FTC. Colon and duodenal biopsies were obtained at baseline (BL) and at 9 months of suppressive ART. Lymphocyte subsets and activation phenotypes ($CD38^+$/$HLA\text{-}DR^+$) were measured in peripheral blood (PB) at BL, month 3, 6, and 9 and in duodenum, and colon at BL and month 9 by flow cytometry. Plasma IL-6, lipoteichoic acid (LTA), sCD14 and zonulin were measured by ELISA. Immunohistochemistry (IHC) of duodenal biopsies was performed to determine T cells/mm^2. Linear mixed models were used to evaluate the association of treatment group with changes in continuous variables.

Results: 26 HIV pts completed the follow-up: 8 on the EFV arm, 10 on the MRV arm and 8 on the MVC+RAL arm. Median age was 37 years [25-42]. Median BL PB CD4 counts were 322, 440 and 453 cell/mm^3, respectively (between-group comparisons, P=ns.). All pts achieved complete HIV suppression.

Levels of IL-6, sCD14 and LTA, but not zonulin, improved during the study (P=0.059, 0.038, 0.006 and 0.304). The MVC+RAL group showed greater improvements of sCD14 (**Figure 1A**, P=0.039) and zonulin (P=0.015) levels. IHC showed that while both CD4 and CD8 T cell density ameliorated in duodenum, the CD4 subset remained far more impaired than

the CD8 subset (between-groups differences, P=ns.). T-cell activation significantly decreased in all compartments during the study, and no differences among groups were appreciated. However, in duodenum, the MVC+RAL group exhibited opposite effects to the EFV group on the naïve/memory CD8 T-cell ratio (**Figure 1B**, P=0.014), %naïve (P=0.018) and activated naïve CD8 T-cells (P=0.001), which increased in the MVC+RAL group but decreased in the EFV group. Similarly, peripheral CCR5+ CD4 and CD8 T cells significantly recovered up to normal levels in the MVC+RAL arm, while decreased in the EFV arm (MVC+RAL vs. EFV, P=0.003 and P=0.002, respectively).

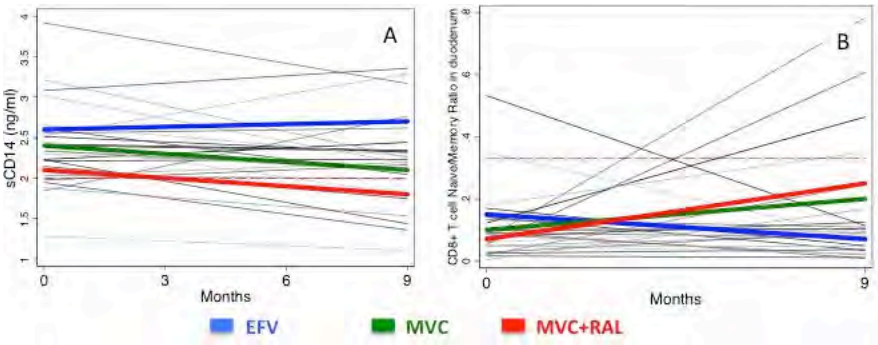


Figure 1. Changes in levels of sCD14 (A) and Duodenal CD8+ Naive/Memory T cell ratio during first-line ART. Individual participant trajectories are represented by grey lines. Dash lines represent levels observed in HIV-uninfected individuals. Red, green and blue lines represent mean changes for each treatment arm predicted by linear mixed-effects models adjusted for baseline CD4 counts. Compared to EFV, RAL+MVC therapy led to a significant decrease of sCD14 levels (P=0.042) (A) and to a significant increase of the CD8+ T cell naive/memory ratio in duodenum (P=0.014) (B).

Conclusions: These data suggest that quadruple ART including RAL+MVC may more effectively reach duodenum and improve systemic markers of innate immune activation and gut barrier. These therapeutic strategies deserve further assessment in clinical trials.

548 Maraviroc-Dependent Pharmacologic Effects on Viral Decay and Immune Recovery in GALT

Corbin Thompson[1]; Tae Wook Chun[2]; Craig Sykes[1]; Zhing-Min Ma[4]; Christopher Miller[4]; Surinder Mann[3]; Richard Pollard[3]; Angela Kashuba[1]; David Asmuth[3]

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, US; [2]Division of AIDS, NIAID, NIH, Bethesda, MD, US; [3]University of California Davis Medical Center, Davis, CA, US; [4]University of California Davis, Davis, CA, US

Background: Immune recovery after antiretroviral (ARV) treatment is incomplete in many tissues such as gut-associated lymphoid tissue (GALT), which may allow for persistent HIV replication. Maraviroc (MVC) and raltegravir (RAL)-based regimens are associated with higher increases in peripheral CD4+ T cells and a more rapid decline in plasma viremia than other regimens, which make them favorable candidates to improve immune recovery and hasten viral decay in GALT. Here, we examine the effect of local ARV concentration on immune and viral dynamics in GALT, and determine whether MVC and/or RAL offer an improvement over NNRTI-based regimens.

Methods: This was a prospective, randomized trial in 26 HIV positive, treatment naïve subjects receiving emtricitabine (FTC) plus tenofovir (TFV) in combination with an NNRTI (efavirenz n=6, nevirapine n=2), MVC (n=10), or MVC + RAL (n=8). Plasma and tissue (duodenum and colon) samples were collected at baseline and 9 months, and CD4+ T cells (flow cytometry), HIV RNA (rtPCR), and intracellular and extracellular drug concentrations (LC-MS/MS) were measured. Paired t-tests and ANOVA were used to assess within- and between-group comparisons, respectively. Associations between variables were made using linear regression. Data are reported as mean change +/- standard deviation; $p<0.05$ was considered significant.

Results: At 9 months, all cohorts showed significant decreases ($p<0.001$) in HIV RNA in plasma (-3.69 ± 0.75 log copies/mL), duodenum (-1.48 ± 1.32) and colon (-3.25 ± 0.99), which were not significant between treatment arms ($p>0.05$). Treatment with MVC+RAL increased duodenal CD4+ T cells from baseline (+106.2 ± 79.1 cells/mm^3, p=0.007). Mean FTC and TFV tissue exposure was 7.2 and 414.7% of plasma and not significant between groups. NNRTI, MVC, and RAL tissue exposure were 407.1, 79.6, and 6.8% of plasma, respectively. Duodenal concentrations of intracellular FTCtp were associated with greater recovery of CD4+ T cells (r=0.91, $p<0.001$) in the MVC cohort and a greater decrease in HIV RNA (r=0.72, p=0.04) in the MVC+RAL cohort.

Conclusions: The restoration of GALT immune cells and reduction in HIV RNA agrees with plasma data, and did not differ between treatment groups. The beneficial effects of FTCtp in the duodenum were observed only in the MVC cohorts, despite all treatment groups having similar concentrations. Taken together, these data suggest that MVC may be an important component of ARV regimens designed to improve virus decay and immune recovery in GALT.

549 Maraviroc Induces HIV Production in RCT and In Vitro, Potentially via the NFkB Pathway

Jori Symons[1]; Ward de Spiegelaere[2]; Annemarie Wensing[1]; Julia Drylewicz[3]; Ananja Middel[4]; Andy I. Hoepelman[4]; Kiki Tesselaar[3]; Linos Vandekerckhove[2]; Steven F. van Lelyveld[4]; **Monique Nijhuis**[1]

[1]University Medical Center Utrecht, Utrecht, Netherlands; [2]Ghent University, Ghent, Belgium; [3]University Medical Centre Utrecht, Utrecht, Netherlands; [4]University Medical Centre Utrecht, Utrecht, Netherlands

Background: Recent data indicated that addition of maraviroc (MVC) to combination antiretroviral therapy (cART) increases immune activation. We investigated MVC induced cell activation and HIV production both in vivo during a MVC intensification trial and in vitro in donor peripheral blood mononuclear cells (PBMCs).

Methods: Using ultra-sensitive droplet digital PCR detailed longitudinal virological and immunological analysis was performed in 15 immune non-responders participating in a 48-week, double-blind, placebo-controlled MVC intensification trial. We assessed changes in total HIV DNA, 2-LTR circles, HIV RNA expression and NF-κB regulated gene expression (TNF-a, IFN-y, IL-10 and IL-6) per million PBMCs. Plasma levels of CCR5 ligands and immune activation markers (IL-2R, IP-10, sICAM and TWEAK) were analyzed by Luminex. Healthy donor PBMCs were infected with X4-tropic virus (HXB2) in absence or presence of increasing MVC levels and CA-p24 production was measured in culture supernatant.

Results: Patient characteristics, immunological and virological baseline values did not differ between the MVC intensification and placebo group. During the first eight weeks of intensification, a significant difference in relative HIV RNA expression was detected (MVC increase 1.7 fold (n=10); placebo decrease 4.2 fold (n=5); p=0.03). After eight weeks we also measured a 2.3 fold increase in plasma CCR5 ligand MIP-1β in the MVC group. During this period, a significant difference in NF-kB regulated gene expression was observed; expression increased in the MVC group and decreased in the placebo group (IFN-y p=0.02; IL-6 p=0.03). No differences in total cellular HIV DNA, 2-LTR circles and plasma activation markers were observed. In vitro assays demonstrated a significant dose-dependent increase in HIV production when MVC was added to PBMCs (2.2 fold). This significant increase in virus production was observed in all experiments (n=9) and at all dosages used (ranging from 1pM–1uM).

Conclusions: MVC intensification of cART in immunological non-responders slightly increases CCR5-ligand expression, NF-κB regulated gene expression and HIV RNA expression. This is in line with our in vitro observation of MVC induced HIV production. Together, these data indicate that MVC induces HIV production, potentially via upregulation of the NF-kB pathway which warrants further investigation into the potential consequences of this observation for the use of MVC as a pre-exposure prophylaxis.

550 Consistency of Dolutegravir Treatment Difference in HIV+ Treatment Naives at Week 96

Catherine M. Granier[1]; **Robert Cuffe**[2]; Louise Martin-Carpenter[3]; Kimberly Y. Smith[3]; Clare Brennan[4]; Keith Pappa[4]; Brian Wynne[4]; Steve Almond[5]; Naomi Givens[1]; Michael Aboud[2]

[1]GlaxoSmithKline, Uxbridge, United Kingdom; [2]ViiV Healthcare, London, United Kingdom; [3]ViiV Healthcare, Research Triangle Park, NC, US; [4]GlaxoSmithKline, Research Triangle Park, NC, US; [5]GlaxoSmithKline, Mississauga, Canada

Background: DTG 50mg QD plus two N(t)RTIs has been compared to 3 preferred regimens in pivotal studies up to 96 weeks (SPRING2 and FLAMINGO) or 144 weeks (SINGLE) in treatment naïve patients. Consistency of the treatment difference was explored within key subgroups.

Methods: SPRING-2 randomized participants to DTG 50mg QD or RAL 400 mg BID, FLAMINGO randomized participants to DTG 50mg or DRV/r QD. In both studies, investigator selected NRTIs (TDF/FTC or ABC/3TC). SINGLE randomized participants to DTG 50 mg + ABC/3TC QD or TDF/FTC/EFV QD. Snapshot response rates were analyzed by NRTI backbone, baseline viral load and baseline CD4. Also, time to efficacy related failure, where withdrawals unrelated to efficacy are censored, were used for the week 96 pooled analyses and were summarised by NRTI backbone and baseline viral load.

Results: The three studies randomized and treated a total of 2139 subjects. Overall, there was no evidence of compromised efficacy in individuals on DTG with high viral load or low CD4s. Subgroup analysis of the Week 96 snapshot suggested that, in individuals with high viral load, there were similar response rates to DTG and EFV in SINGLE however, DTG had a higher response rate vs DRV/r in FLAMINGO. These apparent interactions were not consistent across studies or timepoints. In the SINGLE study, at Weeks 48 and 144, the response rate for patients with high VL at baseline receiving DTG was 7-8 percentage points higher than for those on EFV. Exploratory analyses examining time-to-efficacy related failure showed no difference in response rates between the background NRTIs pooled across the studies irrespective of baseline viral load. Additionally, there was no suggestion of a difference in efficacy related failures between DTG vs comparator agents at high or low viral load.

Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 96 In Snapshot (Primary) Analysis i.e. Missing, Switch or Discontinuation = Failure						
	SPRING-2		SINGLE		FLAMINGO	
	DTG	RAL	DTG	EFV/FTC/TDF	DTG	DRV/r
OVERALL	332/411 (81%)	314/411 (76%)	332/414 (80%)	303/419 (72%)	194/242 (80%)	164/242 (68%)
INDIVIDUALS WITH HIGH BASELINE VIRAL LOAD BY BACKGROUND REGIMEN						
>100,000 c/mL						
ABC/3TC	27/37 (73%)	26/39 (67%)	95/134 (71%)	-	11/13 (85%)	7/12 (58%)
TDF/FTC	62/77 (81%)	47/77 (61%)	-	94/131 (72%)	39/48 (81%)	25/49 (51%)
INDIVIDUALS WITH LOW BASELINE CD4						
<200c/mm3	39/55 (71%)	28/50 (56%)	39/57 (68%)	45/62 (73%)	18/23 (78%)	14/24 (58%)
200 to <350c/mm³	116/144 (81%)	103/139 (74%)	135/163 (83%)	113/159 (71%)	60/73 (82%)	36/51 (71%)
Kaplan Meier estimates of the Proportion of Subjects without Efficacy Related Discontinuation = Failure at Week 96 (PDVF or withdrawal due to lack of efficacy are counted as failure and subjects who discontinue for other reasons are censored)						
	SPRING-2		SINGLE		FLAMINGO	
	DTG	RAL	DTG	EFV/FTC/TDF	DTG	DRV/r
OVERALL	94%	92%	94%	93%	99%	98%
INDIVIDUALS WITH HIGH BASELINE VIRAL LOAD						

Conclusions: In three large treatment-naïve studies, DTG was effective up to week 96 with both ABC/3TC and TDF/FTC, in subjects with high and low viral load and across CD4 strata. DTG is a once daily, unboosted INI that can be used effectively with either TDF/FTC or ABC/3TC backbone in treatment-naive, HIV-infected individuals.

551 Predictors of HIV RNA Suppression on Darunavir/Ritonavir Monotherapy in the MONET and PROTEA Trials

Diego Ripamonti[2]; Ralph DeMasi[3]; **Andrew M. Hill**[1]; Ceyhun Bicer[4]; Christiane Moecklinghoff[5]

[1]Chelsea and Westminster Hospital, London, United Kingdom; [2]A.O. Papa Giovanni XXIII, Bergamo, Italy; [3]Janssen Pharmaceuticals, Inc., Titusville, NJ, US; [4]Janssen Pharmaceuticals, Inc., Beerse, Belgium; [5]Janssen Pharmaceuticals, Inc., Neuss, Germany

Background: In previous studies of protease inhibitor (PI) monotherapy, patients with higher nadir CD4 counts, no HCV co-infection, higher adherence to treatment, or lower baseline levels of HIV RNA or DNA have been the most likely to show sustained HIV RNA suppression <50 copies/mL.

Methods: In the MONET and PROTEA trials, 529 patients with HIV RNA <50 copies/mL at screening switched to DRV/r 800/100 mg once daily, either as monotherapy (n=264) or as triple therapy with 2NRTIs (n=265). Patients with CD4 nadir <100 cells/μL were excluded from these studies. At the screening visit, patients were taking either 2NRTIs plus either NNRTI- based or non-NNRTI based treatment (typically 2NRTI/PI or 2NRTI/Integrase). At Week 48, treatment failure was defined as HIV RNA>50 copies/mL or discontinuation of study drugs (FDA Snapshot method). Multivariate logistic regression was used to identify factors predictive of treatment failure in the two combined clinical trials by Week 48: baseline HIV RNA (target not detected), age, gender, race, HCV co-infection, nadir CD4 count, duration of diagnosis, time to ARV use, treatment group, baseline CD4 count and prior treatment.

Results: In the two trials, there were 224/264 patients on DRV/r monotherapy (85%) with HIV RNA <50 copies/mL at Week 48, versus 240/265 (91%) on triple therapy. In the multivariate logistic regression analysis, the two significant predictors of higher response rates at Week 48 were CD4 nadir ≥200 cells/μL and no prior use of NNRTI-based treatment before baseline. The efficacy of DRV/r monotherapy ranged from 69% for those with CD4 nadir <200 cells/μL and prior NNRTI treatment, to 91% for those with CD4 nadir >200μL and no prior NNRTI treatment (Table). There was no further improvement in efficacy for patients on DRV/r monotherapy with CD4 nadir categories above 200 cells/uL,

CD4 nadir	Prior NNRTI	DRV/r (n=264)	DRV/r + 2NRTI (n=265)
Nadir >=200	no NNRTI	80/88 (91%)	96/99 (97%)
Nadir <200	no NNRTI	36/42 (86%)	34/37 (92%)
Nadir >=200	prior NNRTI	75/86 (87%)	75/88 (85%)
Nadir <200	prior NNRTI	33/48 (69%)	35/41 (85%)
Overall		224/264 (85%)	240/265 (91%)

HIV RNA<50 copies/mL at Week 48, PROTEA/MONET trials

Conclusions: In the combined MONET and PROTEA trials, patients with CD4 nadir above 200 cells/uL and no prior NNRTI-based treatment were most likely to show sustained HIV RNA suppression on DRV/r monotherapy at Week 48 (91%). CD4 nadir may be an indirect marker of prior disease severity.

552 Second-Line Treatment in Sub-Saharan Africa: Week 144 Follow-up of the EARNEST Trial

James G. Hakim[1]; Jennifer Thompson[2]; Cissy M. Kityo[3]; Sarah Walker[2]; Joep van Oosterhout[4]; Anne Hoppe[2]; Andrew D. Kambugu[5]; Peter Mugyenyi[3]; Nicholas Paton[6]
On behalf of the EARNEST Trial Team

[1]University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe; [2]University College London, London, United Kingdom; [3]Joint Clinical Research Centre, Kampala, Uganda; [4]Dignitas, Zomba, Zomba, Malawi; [5]Infectious Disease Institute, Kampala, Uganda; [6]National University of Singapore, Singapore, Singapore; [7]MRC Clinical Trials Unit at University College London, London, United Kingdom

Background: Trials to date have not shown any clear short-term benefit to replacing NRTIs with raltegravir in PI-based second-line therapy. However, longer-term efficacy and safety outcome data are needed to fully assess the potential value of this new combination for ART rollout programme settings.

Methods: 1277 patients aged ≥12 years who met WHO-defined treatment failure criteria after >12 months on NNRTI-based first-line ART were randomised in an open-label trial in 14 sub-Saharan African sites to receive bPI + 2/3 clinician-selected NRTIs (PI/NRTI group), bPI plus RAL (400mg bd) (PI/RAL group); or bPI monotherapy (+RAL induction for first 12 weeks; by DMC recommendation, treatment was re-intensified after week 96 (at median week 124), adding NRTIs only in 94% or by other treatment switch in 6%)(PI-mono group). bPI was standardised to lopinavir/ritonavir, 400mg/100mg bd. Treatment was monitored clinically and by open CD4 count; VL and resistance testing were done annually blinded, reviewed by the DMC. The primary (composite) endpoint, good disease control, was defined as no new WHO stage 4 events (or death) after randomisation, and CD4 count >250 cells/mm3 and VL < 10,000 copies/ml (or >10,000 copies/ml without major/minor PI resistance mutations) at week 96. Here we report final trial outcomes at week 144.

Results: Patients were 58% female, median baseline CD4=71 cells/mm^3, VL=69,782 copies/ml; 2% were withdrawn/lost to follow-up by week 144. There was no evidence of benefit of PI/RAL over PI/NRTI on any efficacy or safety outcome at week 144 (Table 1). In both PI/RAL and PI/NRTI intermediate-high level resistance to lopinavir was low; in PI/NRTI, NRTI resistance was also low (<3.5%); 6.7% of PI/RAL were estimated to have intermediate-high level raltegravir resistance. In PI-mono, clinical and CD4 outcomes were similar to other groups, and VL suppression recovered substantially at week 144 (up from 61.3% <400 c/ml at week 96 to 77.8% at week 144). A substantial proportion of patients in all groups still had not achieved a CD4 >250 cells/mm^3 after 144 weeks on second-line therapy.

	PI/NRTI (n=426)	PI/RAL (n=433)	PI-mono (n= 418)	P value (PI/NRTI vs PI/RAL)	P value (PI/NRTI vs PI-mono)
Good HIV disease control	66%	67%	62%	0.78	0.63
Alive	90.1%	92.4%	92.6%	0.27	0.21
Alive and no new WHO stage 4 events	86.4%	88.9%	88.8%	0.32	0.31
CD4 > 250	77.6%	77.4%	71.9%	0.66	0.57
VL < 1000	87.4%	83.7%	80.2%	0.15	0.008
VL < 400	86.3%	81.4%	77.8%	0.07	0.003
VL < 50	75.1%	71.7%	65.5%	0.28	0.004
Int/high LPV resistance	2.4%	2.7%	11.0%	0.80	<0.001
Int/high NRTI resistance (excl. 3TC/FTC)	3.4%	0.3%	2.5%	0.006	0.51
Int/high RAL resistance	-	6.7%	-	-	-
Grade 3 or 4 AEs	27.5%	27.3%	28.5%	0.89	0.67
SAEs	26.5%	24.5%	23.7%	0.57	0.33

Table: Efficacy and Safety Outcomes at Week 144

Conclusions: PI/RAL was not superior to PI/NRTI at week 144. NRTI re-initiation led to good re-suppression in PI-mono. PI with 2NRTIs remains the optimal regimen for rollout programme settings.

553 Withdrawing Inactive NRTIs in Subjects With Suppressed Viremia: A Randomized Trial

Josep M. Llibre[1]; Hortensia Alvarez[8]; Antonio Antela[2]; Jessica Toro[1]; Juan González-Moreno[3]; M Jesús Perez-Elias[4]; Arkaitz Imaz[5]; Mar Masià[6]; Manel Crespo[7]; Bonaventura Clotet[1]

[1]Univ Hosp Germans Trias, Badalona, Spain; [2]Hospital Clínico Universitario, Santiago de Compostela, Spain; [3]Hospital Son Llàtzer, Mallorca, Spain; [4]Hospital Ramón y Cajal, IRYCIS, Madrid, Spain; [5]Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain; [6]Hospital Universitario de Elche, Elche, Spain; [7]Hospital Universitari Vell d'Hebró, Barcelona, Spain; [8]Complejo Universitario de Ferrol, A Coruña, Spain

Background: Extensively pretreated subjects with virologic failure (VF) may receive salvage regimens containing NRTIs with only residual activity. Once virologic suppression is achieved, their contribution remains elusive. Withdrawing NRTIs with intermediate to complete genotypic resistance (Spanish RIS Resistance Score) when viral load (VL) <50 c/mL could have non-inferior efficacy to their maintenance, with lower potential toxicity and cost.

Methods: Multicenter, randomized, prospective, open study. Subjects with ≥1 prior VF, VL<50 c/mL for ≥ 6 months, any CD4 count, without hep B, receiving ≥2 active drugs (one of them an active boosted PI), and ≥1 NRTI without complete activity, were randomly allocated to stop NRTIs without complete activity (one or both, Exp arm) or to maintain the treatment (Ctrol). No drug changes allowed during last 6 months or at screening. Main endpoint VL<50 c/mL at 48 weeks (Snapshot analysis), non-inferiority margin at -12. EudraCT: 2012-000198-21.

Results: 92 subjects were screened and 90 randomized (Exp, n=45, Ctrol, n=45). Median age 50y old, 80% male, 37% stage C3, 40% chronic hep C, CD4 488 (IQR 355-712) cells, 17 median years on ART. Had received a median of 9 lines of ART, 4 PIs, and a median of 3 (1-4) prior VF. The baseline regimen contained 4 drugs in 46 (51%) subjects, and 3 in 37 (41%). 74 subjects (82%) harbored M184V/I, and the median of TAMs was 3 (2-4; D67X and T215X the most frequent). 32 (71%) subjects removed 1 NRTI (12 TDF, 9 FTC, 8 3TC, 2 ABC, 1 ddI)

and 13 (29%) 2 NRTIs (9 TDF/FTC, 3 ABC/3TC, 1 ABC + TDF). In the primary endpoint, 41/45 (91.1%, Exp) and 44/45 (97.8%, Ctrol) had VL<50 c/mL at 48 weeks (dif 6.7%; 95%CI: -17.4, 4.1). In an analysis allowing NRTI reintroduction, rates of VL <50 c/mL at 48 weeks were 95.6% (Exp) and 97.8% (Ctrol) (dif -2.2% 95%CI: -7.2, 2.7). CD4 cell counts remained stable in both arms. One subject developed VF (confirmed VL>200 c/mL, Exp). New resistance mutations were not selected in genotypic resistance tests. There were 10 grade 3/4 adverse events, 5 in each arm (none related to study drugs). There was one death (lung neoplasia, Exp Arm).

Conclusions: In multitreated patients receiving a successful salvage regimen with at least 2 active drugs (one a boosted PI), the withdrawal of NRTIs without complete activity was safe and associated with high rates of continued virologic suppression at 48 weeks.

554LB Cabotegravir and Rilpivirine As 2-Drug Oral Maintenance Therapy: LATTE W96 Results

David A. Margolis[1]; Cynthia C. Brinson[2]; Graham H. Smith[3]; Jerome de Vente[4]; Debbie P. Hagins[5]; Sandy K. Griffith[1]; Marty H. St. Clair[1]; Kimberly Y. Smith[6]; Peter E. Williams[7]; William R. Spreen[1]

[1]GlaxoSmithKline, Durham, NC, US; [2]Central Texas Clinical Research, Austin, TX, US; [3]Maple Leaf Medical Clinic, Toronto, Canada; [4]Living Hope Foundation, Long Beach, CA, US; [5]Chatham County Health Department, Savannah, GA, US; [6]ViiV Healthcare, Durham, NC, US; [7]Janssen Pharmaceuticals, Inc, Beerse, Belgium

Background: Cabotegravir (CAB, GSK744) is an HIV INSTI under development as both an oral and long-acting (LA) injectable. LATTE was designed to select an oral dose of CAB and to evaluate a two-drug ART regimen with rilpivirine (RPV), as suppressive maintenance therapy.

Methods: Phase 2b, multicentre, partially-blinded, dose-ranging study in ART-naïve HIV infected adults, randomized 1:1:1:1 to the induction regimen of once daily oral CAB 10 mg, 30 mg, 60 mg or efavirenz (EFV) 600 mg with TDF/FTC or ABC/3TC through Week (W) 24, followed by a two-drug oral maintenance regimen of CAB (blinded dose) + RPV 25 mg through W96. CAB patients (pts) with a VL <50 c/mL immediately prior to W24 discontinued NRTIs and began RPV 25 mg; no change was made for EFV + NRTIs pts (ITT-Maintenance Exposed (ME)).

Results: 243 pts were randomized and treated (ITT-E): 96% male, 38% non-white, 14%>100,000 c/mL HIV-1 RNA, 61% TDF/FTC. Amongst pts who began CAB + RPV at W24, 86% had HIV-1 RNA <50 c/mL by snapshot at W96 overall, relative to 83% of pts continuing EFV (ITT-ME). Five protocol-defined virologic failures occurred during 72 weeks of Maintenance (CAB 10 mg [2], CAB 30 mg [1], EFV [2] including two on CAB + RPV with treatment emergent resistance [INI + NNRTI, NNRTI]). Drug-related AEs ≥ Grade 2 were reported by 14% and 19% of CAB and EFV pts, respectively with 4% and 4% occurring during the 72W Maintenance phase. SAEs occurred in 10% of CAB pts (none drug related); and 6% EFV pts (one drug-related - suicide attempt). Fewer CAB pts withdrew due to AEs (3%), than EFV pts (15%), mostly prior to the Maintenance phase. Treatment-emergent lab abnormalities ≥ Grade 3 occurred in 26% of CAB and 37% of EFV pts through W96, most commonly elevated creatine kinase. Rates of any graded ALT elevations were 20% with CAB and 21% with EFV.

Snapshot Study Outcomes	CAB 10 mg (n=60)	CAB 30 mg (n=60)	CAB 60 mg (n=61)	CAB Subtotal (n=181)	EFV Control (n=62)
%<50c/mL at W96 Snapshot (ITT-E) (95%CI)++	41 (68%) (57%,80%)	45 (75%) (64%,86%)	51 (84%) (74%,93%)	137 (76%) (69%,82%)	39 (63%) (51%,75%)
Protocol-defined Virologic Failure	3 (5%)	2 (3%)	1 (2%)	6 (3%)	6 (10%)
Failure due to Adverse Event	1 (2%)	1 (2%)	4 (7%)	6 (3%)	9 (15%)
Failure due to HIV-1 RNA ≥50 c/mL¥	5 (8%)	1 (2%)	2 (3%)	8 (4%)	2 (3%)
Failure due to Other Reasons While Not Suppressed+	2 (3%)	2 (3%)	1 (2%)	5 (3%)	3 (5%)
Failure due to Other Reasons While Suppressed+	8 (13%)	9 (15%)	2 (3%)	19 (10%)	3 (5%)
Other Results					
<50 c/mL at W96 Snapshot (ITT-ME)	41/52 (79%)	45/53 (85%)	51/55 (93%)	137/160 (86%)	39/47* (83%)
Grade 2-4 Drug Related AEs	5 (8%)	8 (13%)	13 (21%)	26 (14%)	12 (19%)
Median Baseline CD4+ cells/mm3 (Change from Baseline at W96)	415.0 (236.5)	404.0 (249.5)	420.0 (271.5)	412.0 (259.5)	416.5 (289.0)

¥ HIV-1 RNA ≥50 c/mL reasons include HIV-1 RNA ≥50c/mL at Week 96 or discontinued while not suppressed (≥50 c/mL) for Lack of Efficacy + Other reasons include missing data; protocol deviation, non-compliance, lost to follow-up, withdrawn consent, investigator discretion, ART change, and ineligible for Maintenance phase ++W96 represents a 24 Week Induction phase followed by a 72 Week Maintenance phase *EFV pts with a W24 visit (n=47) Intent to Treat-Exposed (ITT-E) and Intent to Treat- Maintenance Exposed (ITT-ME)

Conclusions: When used as two-drug maintenance therapy in virologically suppressed pts, CAB + RPV provided similar antiviral activity to EFV+2 NRTIs through W96. CAB + RPV was well tolerated overall, with no SAEs considered drug related and few AEs leading to withdrawal. Considering all safety and efficacy data, oral CAB 30mg once-daily was selected for further development. Results support the selected dose regimens for the ongoing Ph2 LATTE-2 study with CAB LA + RPV LA as injectable two-drug maintenance therapy.

TUESDAY, FEBRUARY 24, 2015

Session P-K1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

ART: Adherence, Adherence, Adherence

555 Self-Reported Versus Blood-Tested ART Intake to Estimate ART Coverage in South Africa

Helena Huerga[1]; Gilles Van Cutsem[2]; Lubbe Wiesner[3]; Malika Bouhenia[1]; Jihane Ben Farhat[1]; Emmanuel Fajardo[2]; Ruggero G. Giuliani[2]; David Maman[1]; Thomas Ellman[2]; Jean-François Etard[1]

[1]Epicentre, Paris, France; [2]Médecins Sans Frontières, Cape Town, South Africa; [3]University of Cape Town, Cape Town, South Africa

Background: Reliable information on ART intake is essential to estimate ART coverage and interpret HIV resistance. In the context of a population-based HIV survey in Mbongolwane and Eshowe, KwaZulu-Natal, South Africa, we assessed self-reported versus blood-tested ART intake agreement and we estimated ART coverage using both measurements.

Methods: Cross-sectional population-based survey. Persons aged 15-59 years were eligible. Face-to-face interviews were followed by rapid HIV testing on site and blood collection for ART testing and other HIV-related tests. Qualitative ART testing for nevirapine, efavirenz and lopinavir covered all ARV regimens in the public sector and detected drugs down to 0.2 μg/ml. ART coverage was defined as the proportion of HIV positive on ART among those eligible according to National Guidelines.

Results: In total, 5649/6688 (84.5%) individuals were included. Overall HIV prevalence was 25.2% (95%CI: 23.6-26.9). Self-reported vs blood-tested ART intake agreement was 91.9% (kappa=0.84). In total, 58/741 (7.8%) participants with a positive blood test declared not taking ART and 52/712 (7.3%) self-reporting ART intake had a negative blood test (table). ART intake agreement was similar in women and men: 91.9% (kappa=0.84) vs 92.0% (kappa=0.84) and lower in those aged <25 years compared to ≥25 years: 88.4% (kappa=0.70) vs 92.6% (kappa=0.85). Among individuals <25 years: 15/64 (23.4%) with positive blood test declared no ART and 12/61 (19.7%) with negative blood test self-reported ART intake. ART coverage was 75.0% using blood-tested ART and 72.1% using self-reported ART. Viral load was ≥1000 cp/ml in 17/57 (29.8%) with negative self-report and positive blood-test and 39/52 (75.0%) with positive self-report and negative blood-test. Resistance to ARV was found in 33 (61.1%, 95%CI: 47.2-73.4) of the 54 individuals with viral load ≥1000 cp/ml who self-reported ART intake. Of them, 12 (36.4%) had a negative ART blood test.

	ART blood-tested			
ART self-reported	Positive	Negative	Missing	Total
Yes	655	52	5	712
No	58	593	22	673
Missing	28	10	0	38
Total	741	655	27	1423

Self-reported and blood-tested ART intake among HIV positive participants

Conclusions: Self-reported and blood-tested ART agreement was high in the overall population but lower among young people. Stigma related issues may explain some of the measurement differences found in young people. Overall ART coverage estimations were not affected by the measurement discrepancies. ART self-reporting can be a good tool for overall ART coverage estimations. However, blood testing for ART is preferable when assessing ART intake in young people and should be taken in consideration when interpreting ART resistance.

556 Real-Time Electronic Adherence Monitoring and Risk of Viral Rebound

Jessica E. Haberer[1]; Nicholas Musinguzi[2]; Mark Siedner[1]; Yap Boum[3]; Peter W. Hunt[4]; Jeffrey Martin[4]; David R. Bangsberg[1]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]Mbarara University of Science and Technology, Mbarara, Uganda; [3]Médecins Sans Frontières, Mbarara, Uganda; [4]University of California San Francisco, San Francisco, CA, US

Background: While sustained adherence to antiretroviral therapy (ART) is known to be critical for viral suppression, the risk of viral rebound associated with any given adherence interruption is poorly understood. We used real-time adherence monitoring and HIV RNA measurement during adherence interruptions to understand the characteristics of interruptions that predict viral rebound.

Methods: The Ugandan AIDS Rural Treatment Outcomes Study (UARTO) is an observational cohort of adults initiating ART. Procedures include 4-monthly assessment of HIV RNA and adherence monitoring with a wireless device that transmits a cellular signal with each opening (Wisepill). If no signal is received for 48+ hours, research staff visit participants' homes unannounced to ascertain the cause and collect blood for HIV RNA measurement. For participants with prior viral suppression (<400 copies/ml), we fit generalized estimating equation logistic regression models to identify predictors of rebound viremia during adherence interruptions.

Results: We monitored 470 participants between June 2011 and January 2014; 72% were women, median age was 35 years (IQR 28-42), baseline CD4 was 198 cells/mm^3 (IQR 110-294), pre-ART HIV RNA was 5.0 $\log_{10}$ copies/ml (IQR 4.5-5.5) and median duration of prior viral suppression was 13 months (IQR 3-48). Overall median adherence was 97% (IQR 90-100%). We observed 4,447 interruptions lasting 48+ hours; median duration was 2.8 days (IQR 2-4.2). Participants had a median of 1 interruption per month (IQR 1-1). The following interruptions were excluded from analysis: 3,303 (74%) had no blood drawn for HIV RNA assessment (i.e., participant restarted ART prior to investigation, participant declined, technical cause of the interruption), 447 (10%) were missed, and 127 (3%) had detectable HIV RNA prior to the interruption. Of the remaining 570 (13%) interruptions, 14 (2%) revealed new viral rebound. Predictors of viral rebound are shown in the table. No interactions were seen. All but 9 interruptions (561/570; 99%) ended with the investigation and 11/14 (79%) had re-suppressed HIV RNA on subsequent testing.

	Univariable OR (95% CI)	Multivariable AOR* (95% CI)
Duration of lapse (days beyond 48 hours)	**1.27 (1.08-1.49) p=0.004**	**1.29 (1.04-1.60) p=0.025**
Prior duration of viral suppression (years)	0.71 (0.49-1.03) p=0.071	**0.56 (0.36-0.88) p=0.011**
30-day adherence prior to interruption (10% increments)	**0.74 (0.56-0.97) p=0.030**	0.76 (0.56-1.04) p=0.082
Pre-treatment HIV RNA	0.99 (0.99-1.00) p=0.55	-
Regimen backbone– nevirapine	*(ref)*	*(ref)*
efavirenz	**0.17 (0.04-0.82) p=0.027**	**0.05 (0.01-0.31) p=0.001**
	*Model may be overfit	Bold = p<0.05

Predictors of viral rebound

Conclusions: While each day of adherence interruption increases risk of viral rebound, increased duration of prior viral suppression and use of long-half life medication (efavirenz) are protective. This analysis is limited by the small number of interruptions. Re-suppression of most terminated interruptions is promising proof-of-concept support for real-time adherence intervention.

557 Determinants of Adherence to Antiretroviral Therapy Differ Between Africa and Asia

Rimke Bijker[1]; Awachana Jiamsakul[2]; Margaret Siwale[3]; Sasisopin Kiertiburanakul[4]; Cissy M. Kityo[5]; Praphan Phanuphak[6]; Tobias F. Rinke de Wit[1]; Oon Tek Ng[7]; Raph L. Hamers[1]; PASER-TASER Cohort Collaboration[1]
PASER-TASER Cohort Collaboration

[1]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands; [2]The Kirby Institute, Sydney, Australia; [3]Lusaka Trust Hospital, Lusaka, Zambia; [4]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [5]Joint Clinical Research Centre, Kampala, Uganda; [6]HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [7]Tan Tock Seng Hospital, Novena, Singapore

Background: Adherence to antiretroviral therapy (ART) has been poorly studied among HIV-infected populations in resource-limited settings. We studied determinants of adherence in sub-Saharan Africa and Asia.

Methods: In a cohort collaboration in Africa (6 countries, 13 sites) and Asia (5 countries, 11 sites) adherence was assessed using the WHO-validated Adherence Visual Analogue Scale (VAS) at each clinic visit, during the first 24 (all sites) or 36 (15 sites) months of 1st-line ART. The main outcome was suboptimal mean adherence (SubAdh), defined as mean VAS<95% for each 6-month period. We used generalized estimating equations multivariable regression, adjusting for number of adherence assessments, site type and calendar year. Region-of-residence was assessed as a potential effect modifier.

Results: In the first 24 months of follow-up, 23,074 VAS assessments were performed in 3,913 participants; median per participant was 7 (IQR 6-8) in Africa (n=2,409) and 8 (IQR 5-9) in Asia (n=1,504). Of 12,889 mean adherence scores, 6.5% (832/12,889) were classified as SubAdh, with 7.3% (614/8,398) in Africa versus 4.9% (218/4491) in Asia (Chi2, p<0.001) (**Figure**). SubAdh was strongly associated with virological failure (≥400 c/mL) at month 12 and 24 (Chi2, p<0.001). In Africa (but not in Asia), factors associated with SubAdh were male sex (OR 1.4, 95%CI 1.1-1.6) and any concomitant medication (1.9, 1.2-3.1); attending a non-government facility (0.7, 0.5-0.9) and older age were associated with less SubAdh. In Asia, relative to heterosexuals, SubAdh was lower in men who have sex with men (0.5, 0.3-0.9) and higher in injecting drug users (3.5, 2.1-5.8). In both regions, longer ART duration (extending to at least 36 months) was associated with better adherence. A sensitivity analysis that accounted for attrition, using last observation carried forward methods, suggested that adherence improvement with ART duration was not entirely due to attrition bias or missing data. Type of ART regimen was not associated with SubAdh. Participants from high or upper-middle income countries had a 24% (95%CI 7-38%) reduced risk of SubAdh, compared to low or lower-middle income countries (p=0.007).

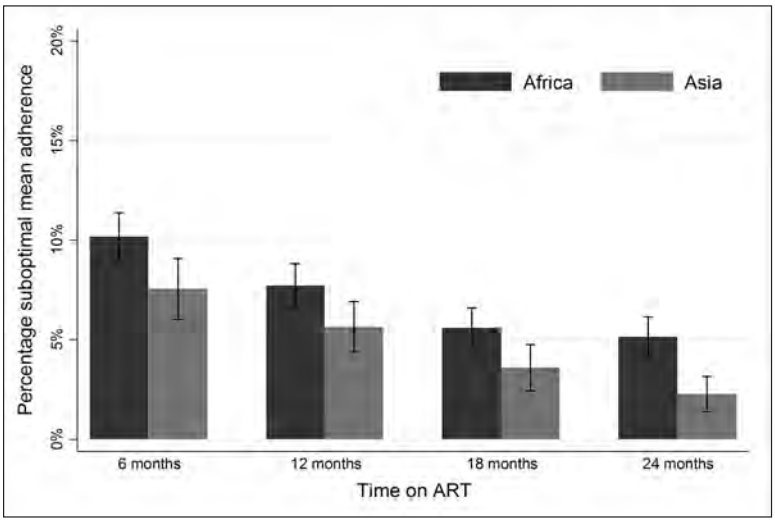


Figure. Suboptimal adherence over time across regions in participants who initiated first-line ART (n=3913)

Conclusions: Cross-regional differences may be partly related to health system resources, although social desirability bias cannot be excluded. Interventions to improve adherence need to be locally tailored and should particularly target the first ART years.

558 Retention on Antiretroviral Therapy by Sex and Pregnancy Status in a Large Cohort of HIV-Infected Patients in Rural Nigeria

Usman I. Gebi[2]; Meridith Blevins[1]; Mukhtar Y. Muhammad[2]; C. William Wester[1]; Muktar H. Aliyu[1]

[1]Vanderbilt University, Nashville, TN, US; [2]Friends for Global Health Initiative Nigeria, Abuja, Nigeria

Background: To examine whether differences exist in retention on antiretroviral therapy (ART) by sex and pregnancy status in a cohort of HIV-infected patients enrolled in a HIV treatment program in rural north-central Nigeria.

Methods: We used routine program data collected from June 2009–September 2013. The study population included HIV-infected ART-naïve patients entering care and treatment (age ≥15 years). Kaplan-Meier and cumulative incidence estimates were calculated for early ART initiation and loss-to-follow up (LTFU) by sex and pregnancy status.

Results: and loss-to-follow up (LTFU) by sex and pregnancy status.

A total of 3,813 ART-naïve clients (68% women, 11% of whom were pregnant) were enrolled into care during the study period. The median CD4+ cell count for all clients was 232 cells/μL [interquartile range (IQR): 114-390]; 29% of clients had advanced disease (WHO clinical stage 3/4). Pregnant women had higher median CD4+ cell counts (306 cells/μL [IQR: 174-475] than non-pregnant women (244 cells/μL [IQR: 121-415]), and men (197 cells/μL [IQR: 91-328]), p<0.001. The proportion of pregnant clients initiating ART within 90 days of enrollment (78%, n=213) was significantly higher than the corresponding proportion of non-pregnant women (54%, n=1261) and men (53%, n=650), p<0.001. Pregnant women initiated ART twice as fast as non-pregnant women and men (median [IQR] days from enrollment to ART initiation for pregnant women = 7 days [0-21] vs. 14 days [7-49] for non-pregnant women and 14 days [7-42] for men). No significant difference was observed between the groups in cumulative incidence of LTFU during the first 12 months following ART initiation (66% of pregnant women vs. 65% of non-pregnant women and 67% of men), p=0.79.

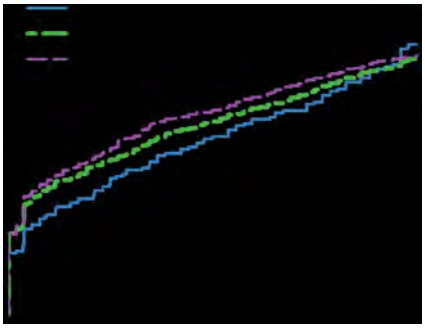


Figure: Cumulative incidence of loss to follow up during the first 12 months following cART initiation by sex and pregnancy status at enrollment, VU/FGH Nigeria program (for individuals who were initiated on cART within 90 days of enrollment, n= 2124).

Conclusions: Pregnancy status had a favorable impact on early ART initiation, but did not influence 1-year retention rates in this large cohort of HIV-infected patients in rural Nigeria. These findings highlight the importance of addressing retention across all patient groups, regardless of sex and pregnancy status.

559 Randomised Controlled Trial of Text-Message Dosing Reminders in Patients Starting ART

Catherine Orrell[1]; Karen Cohen[1]; Katya Mauff[1]; David R. Bangsberg[2]; Gary Maartens[1]; Robin Wood[1]

[1]University of Cape Town, Cape Town, South Africa; [2]Harvard Medical School, Boston, MA, US

Background: Some studies have shown that antiretroviral therapy (ART) adherence could be improved with mobile phone text message reminders, while other studies have shown that patients rapidly habituate to reminders. We hypothesized that text message reminders, sent only when dosing is late, as recorded by real-time electronic adherence monitoring devices (EAMD), would improve adherence and HIV viral suppression over 48 weeks compared to standard of care (SoC).

Methods: The study was conducted in an outpatient ART clinic in South Africa. ART-naïve participants were randomised (1:1) to SoC, including three pre-treatment group education sessions, or intervention, which comprised SoC with the addition of an automated text message reminder to their mobile phone if dosing was >30 minutes late. Staff and participants were not blinded to study arm. All participants were given EAMD at ART start and followed for 48 weeks. Bloods for CD4 cell count and viral load were drawn at baseline, weeks 16 and 48. Outcomes included the proportion of doses taken over the time on study as recorded by EAMD, and plasma HIV-1 viral load suppression (<40 copies/ml) at week 48. The analysis was intention to treat (missing=failure). The trial was registered with the Pan African Clinical Trial Registry: PACTR201311000641402.

Results: Between July 2012 and March 2013, 230 participants were randomly assigned to the standard of care (n=115) or intervention (n=115) arms. Median adherence by EAMD was 82.1% (IQR 56.6-94.6%) in the intervention arm, compared to 80.4% (IQR 52.8-93.8%) in the SoC arm (aOR for adherence 1.08, 95%CI: 0.77-1.52, p=0.642). Suppressed viral loads (<40 copies/ml) were seen in 80 (69.6%) of control and 75 (65.2%) of intervention (missing = failure; aOR for virological failure in intervention arm 0.77, 95%CI: 0.42-1.40, p=0.393) at week 48.

Generalised linear model (GLM) of cumulative adherence by EAMD over time on study.

Generalised linear models				No. of observations: 230 Link function: Logit
Adherence	Odds Ratio	Std. Error	p-value	95% Confidence Interval
Intervention arm	1.08	0.19	0.642	0.77 - 1.52
Age*	1.02	0.01	0.014	1.00 - 1.04
Anxiety score >8	1.05	0.19	0.797	0.74 - 1.49
Depression score >8	0.74	0.14	0.100	0.51 - 1.06
CD4	1.00	0.00	0.699	1.00 - 1.01
Male sex	0.96	0.17	0.802	0.68 - 1.34
Non-disclosure	0.72	0.30	0.368	0.32 - 1.63
Screen CAGE ≥2	1.05	0.45	0.819	0.67 - 1.67

*The number of pills taken, relative to the number of pills not taken, increases by 27% for each 10 year increase in age: OR 1.27 (95%CI 1.05-1.52).

Conclusions: Text message reminder linked to late doses detected by real-time adherence monitoring did not significantly improve adherence or HIV viral suppression.

560 Socioeconomic Factors and Virological Rebound: A Prospective UK Cohort Study

Lisa S. Burch[1]; Colette Smith[1]; Jane Anderson[3]; Lorraine Sherr[1]; Alison Rodger[1]; Richard Gilson[1]; Jonathan Elford[2]; Andrew N. Phillips[1]; Margaret Johnson[4]; Fiona Lampe[1]
ASTRA (Antiretrovirals, Sexual Transmission Risk and Attitudes)

[1]University College London, London, United Kingdom; [2]City University London, London, United Kingdom; [3]Homerton University Hospital NHS Foundation Trust, London, United Kingdom; [4]Royal Free London NHS Foundation Trust, London, United Kingdom

Background: Little is known about the effect of social deprivation on HIV treatment outcomes in the UK, a setting with universal free access to health care. We assessed the association of socio-economic factors with subsequent virological rebound among individuals with initial virological suppression on ART.

Methods: ASTRA is a questionnaire study of 3258 HIV-diagnosed individuals from 8 UK HIV clinics in 2011/2012, with longitudinal linkage to clinical records for consenting participants (92%) at 4 clinics. We included those who had received ART for >6 months, had viral load (VL)≤50 c/mL at the time of the questionnaire (baseline) and with ≥1 subsequent VL measure. Individuals were followed from baseline until virological rebound (1st VL>200 c/mL) or last available VL (latest April 2014). Self-reported non-adherence was defined as the number of times ≥2 consecutive days of ART was missed in the 3 months prior to baseline (0; 1; ≥2). Follow-up was not censored if ART was interrupted. We assessed the association of each socio-economic factor (financial hardship, employment, housing, education, time in UK, English reading ability, supportive network) with virological rebound in a separate Cox regression model, adjusted for (i) demographic factors (gender/sexual orientation; ethnicity; age; clinic); (ii) demographic factors and baseline non-adherence. Sensitivity analyses considered rebound as 2 consecutive VL>200 c/mL.

Results: 1490 people were followed for 2710 person-years [median 3 (range 1-17) VL measures per person]. 65 (4%) people experienced virological rebound (rate 2.4/100 pyrs; 95% CI 1.8-3.0). Kaplan-Meier percentages with rebound by 12 and 24 months were 2.0% (95% CI 1.3-2.8) and 4.8% (3.5-6.0). After adjustment for demographic factors, increasing financial hardship, non-employment, non-homeownership, non-university education and lack of supportive network were associated with higher risk of rebound (Table). Although further adjustment for baseline non-adherence did not fully explain the associations, they were attenuated (Table). Sensitivity analysis results were consistent (37 rebounds).

				Adjusted for demographics*			Adjusted for demographics* and non-adherence#		
Socio-economic factor[x]		N	Rate~	aHR	95% CI	p	aHR	95% CI	p
Money for basic needs? (Financial hardship)	Always	717	1.29	1		0.0051^	1		0.0503^
	Mostly	380	2.85	1.63	(0.83, 3.22)		1.68	(0.85, 3.33)	
	Sometimes	223	3.29	2.06	(0.97, 4.39)		1.49	(0.68, 3.28)	
	No	143	6.17	2.93	(1.35, 6.38)		2.35	(1.06, 5.22)	
Employed	Yes	844	1.23	1		<.0001	1		0.0005
	No	646	3.93	3.64	(2.02, 6.58)		2.94	(1.60, 5.39)	
Homeowner	Yes	574	0.56	1		0.0005	1		0.0011
	No	891	3.72	4.70	(1.97, 11.20)		4.28	(1.79, 10.24)	
University education	Yes	651	1.57	1		0.0196	1		0.0390
	No	804	2.94	2.05	(1.12, 3.75)		1.90	(1.03, 3.50)	
Time in UK	Born in UK	869	2.09	1		0.4706	1		0.2988
	In UK >5 years	521	2.87	0.69	(0.34, 1.41)		0.61	(0.29, 1.29)	
	In UK ≤5 years	52	4.47	1.18	(0.39, 3.58)		1.26	(0.42, 3.77)	
Reading ability	Born in UK	869	2.09	1		0.6962	1		0.5733
	Fluent	489	2.83	0.74	(0.37, 1.49)		0.71	(0.35, 1.47)	
	Not fluent	89	3.86	0.81	(0.27, 2.44)		0.62	(0.21, 1.83)	
Supportive network	Most support	884	1.61	1		0.0006^	1		0.0184^
	Medium support	448	3.14	1.98	(1.11, 3.53)		1.51	(0.83, 2.74)	
	Least support	142	4.73	3.12	(1.55, 6.27)		2.36	(1.15, 4.84)	

Table: Association between socio-economic factors and virological rebound

([x] each socio-economic factor considered in a separate model for all results;* gender/sexual orientation, ethnicity, age and clinic; [#] self-reported number of times ≥2 consecutive days of ART missed in 3 months prior to baseline (0; 1; ≥2); ~ per 100 person-years; ^ test for trend; aHR=adjusted Hazard Ratio)

Conclusions: Even in this setting with free access to treatment and low rates of virological rebound, we observed a substantial impact of social deprivation on increased risk of rebound among people with initial virological suppression. These associations are likely mediated through non-adherence. Targeted adherence interventions and increased social support for those most at risk should be considered.

TUESDAY, FEBRUARY 24, 2015

Session P-K2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

ART: Monitoring and Biomarkers

561 New Marker of Standard-of-ART Care: Percentage of Time on cART With Suppressed HIV-RNA

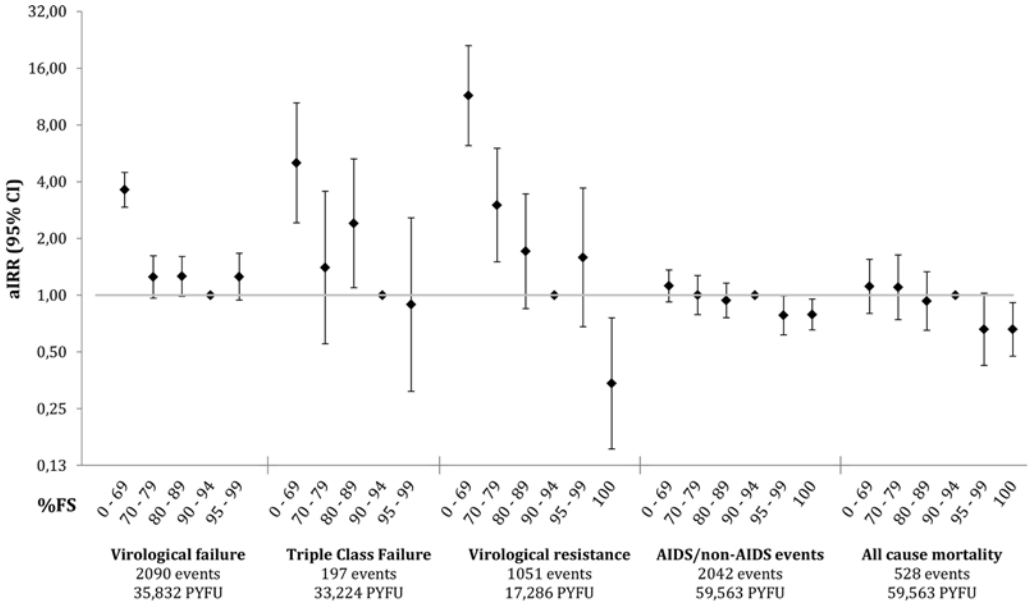
Kamilla G. Laut[1]; Leah C. Shepherd[4]; Court Pedersen[2]; Jürgen Rockstroh[3]; Helen Sambatakou[5]; Dzmitry Paduta[6]; Jens D. Lundgren[1]; Amanda Mocroft[4]; Ole Kirk[1]; EuroSIDA in EuroCoord[1] on behalf of EuroSIDA in EuroCoord

[1]*Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;* [2]*Odense University Hospital, Odense, Denmark;* [3]*University Hospital Bonn, Bonn, Germany;* [4]*University College London, London, United Kingdom;* [5]*Hippokration General Hospital, University of Athens, Athens, Greece;* [6]*Gomel Regional Centre for Hygiene, Gomel, Belarus*

Background: A WHO recommended indicator of standard-of-care for ART is proportion of individuals fully suppressed 48 weeks after ART initiation. As this is a measure of short term outcome and ART is required life-long, there is a need to consider whether other indicators are better to evaluate ART treatment programs. We evaluated a novel indicator that captures the percentage of time treated being fully suppressed (%FS) for various ART-related outcomes, in order to establish which degree of %FS is required for optimal outcome.

Methods: Follow-up time for patients on cART followed in EuroSIDA after January 2001 and with ≥3 VL measurements after baseline was classified for %FS. %FS (HIV-RNA<50copies/mL) was assessed, censoring the first 4 months after initiation or change of cART due to VF, to allow full suppression to occur. Follow-up was until death or last follow-up, and multiple events were allowed (not for TCF or death). %FS was then associated, using Poisson regression adjusted for demographics, HIV- and non-HIV-related risk factors, with following endpoints: *Virological Failure (VF)*: 2 consecutive HIV-RNA≥500 copies/mL; *Triple Class Failure (TCF)*: HIV-RNA≥500 copies/mL while on cART including 2 NRTIs, 1 NNRTI or 1 PI(/r); *Resistance*: any new NRTI, NNRTI or major PI-mutation, *Fatal/non-fatal AIDS/non-AIDS events* and *All-Cause Mortality*.

Results: 11,980 patients contributed with a median follow-up time of 4.5 [IQR 1.9-7.6] years and 14 [6-24] VL-measurements. 25% were female, median age was 40.9 [35.3-48.1] years, CD4 cell count at baseline 428 [282-605]/mm^3, and median %FS 93.6 [74.1-100]%. Adjusted incidence rate ratios (aIRRs) tended to increase above 1 for lower %FS for all endpoints evaluated, compared with %FS 90-94% (Fig). The threshold for significantly elevated risk however differed depending on the endpoint evaluated from below 70% (VF aIRR 3.61 [95%CI 2.91-4.47]), to 80% (resistance aIRR 3.01 [1.50-6.02]), to 90% for TCF (aIRR 2.41 [1.10-5.28]) and to 95% for new clinical events aIRR 0.78 [0.62-0.99] and death aIRR 0.66 [0.42-1.02].



Adjusted incidence rate ratios (aIRR) for percentage of time on cART spent fully suppressed (%FS). Adjusted for age (per 10 years older), gender, body mass index, smoking status, risk group, ethnicity, region of residence, current CD4, cumulative years on ART, current PI use, current NNRTI use, cumulative number of ARVs used historically, prior AIDS event, prior non-AIDS event (cardiovascular, end stage liver disease, non-AIDS defining malignancy, pancreatitis), prior HBV or HCV, diabetes, and hypertension. Resistance models also adjusted for prior resistance. Relative distribution of PYFU within %FS strata was similar for all endpoints (e.g. all-cause mortality, 0-69, 70-79, 80-89, 90-94, 95-99 and 100%): 23.9, 7.0, 12.3, 9.1, 7.7 and 39.9% , respectively.

Conclusions: Living more than 95% of time on ART fully suppressed provides the best outcome from use of ART. If %FS is 80-95% this provides reasonable outcome, whereas %FS below 80% provides suboptimal outcome. %FS is a novel indicator to evaluate ART programs, warranting further examination, that may provide a more comprehensive picture of standard-of-ART-care than existing WHO evaluation criteria, and will aid further improvement in quality of care efforts.

562 Viremia Copy Years and Its Impact on Risk of Clinical Progression According to Shape

Alessandro Cozzi-Lepri[1]; Antonella Cingolani[2]; Andrea Antinori[3]; Andrea De Luca[4]; Cristina Mussini[5]; Stefano Rusconi[6]; Carmela Pinnetti[3]; Massimo Galli[6]; Antonella Castagna[8]; Antonella d'Arminio Monforte[7]

[1]University College London, London, United Kingdom; [2]Sacro Cuore University, Roma, Italy; [3]INMI Spallanzani, Roma, Italy; [4]University of Siena, Siena, Italy; [5]University of Modena, Modena, Italy; [6]Luigi Sacco University Hospital, Milano, Italy; [7]S. Paolo Hospital, Milano, Italy; [8]San Raffaele Scientific Institute, Milano, Italy

Background: Viremia copy-years (VCY), a measure of cumulative HIV burden approximated by the area under a patient's viral load (VL) curve (AUC), was shown to predict mortality independently of VL and current CD4 count in ART-treated patients. For a given AUC, its shape (e.g. a VL of 10,000 copies/mL for 1 year) might help identifying patients (pts) whose VL/ART history differ from that of pts with other shapes (e.g. a VL of 1,000 copies/mL for 10 years).

Methods: All pts who were enrolled in the Icona Foundation study and who started cART after January 1, 2000 were included. VCY (log10 scale) was calculated using the trapezoidal rule. Cox proportional hazards regression model was used to estimate the relationship between VCY and two endpoints (AIDS/death and severe non-AIDS[SNAE]/death) with time accruing from ART initiation. Multivariable models were constructed both controlling for CD4 count as time-updated covariate and using inverse probability weights (IPW). Pts were classified according to the quartiles of the proportion of AUC over the maximum rectangular with base the length of VL follow-up and height pts' ever observed VL peak under ART. Roughly, a proportion of 100% identifies patients with stable VL trajectory at peak level while low percentages people with dips and spikes in VL.

Results: We included 5,376 pts in Icona with the following characteristics: 36% MSM, 84% of Italian nationality with median (range) age of 37 (18-78) years, who started cART on average in 2010, 54% started PIr-based cART. By the end of follow-up median (IQR) of VCY was 5.27 (2.69-11.19 log10 copies/mL). The quartiles of the VCY distribution identified the following groups: A: 0-35%, B: 36-40% C: 41-55% and D: 56+% of maximum rectangular. We observed 175 AIDS, 187 SNAE and 69 deaths. The magnitude of risk associated with 1 log10 higher VCY was under-estimated when controlling for CD4 as time-updated covariate vs. IPW (e.g. for AIDS/death HR=1.10 vs. HR=1.19). Results of the stratified analysis are shown in Table.

	Hazard Ratio of AIDS/death (95% CI)		
	Unadjusted	Adjusted*	p-value#
VCY (per log10 copies/mL higher)			<.001
Shape A[1]	0.89 (0.77, 1.04)	0.88 (0.76, 1.01)	
Shape B[2]	0.95 (0.84, 1.07)	0.95 (0.84, 1.06)	
Shape C[3]	1.01 (0.93, 1.10)	0.99 (0.90, 1.08)	
Shape D[4]	1.24 (1.18, 1.31)	1.24 (1.17, 1.31)	
	Hazard Ratio of SNAE/death (95% CI)		
Shape A[1]	0.78 (0.56, 1.08)	0.78 (0.58, 1.05)	0.01
Shape B[2]	0.97 (0.85, 1.10)	0.96 (0.84, 1.09)	
Shape C[3]	0.92 (0.81, 1.03)	0.90 (0.79, 1.02)	
Shape D[4]	1.12 (1.05, 1.19)	1.10 (1.03, 1.16)	

*Adjusted for age, mode of HIV transmission, nationality, calendar year of starting ART and time-updated CD4 count using IPW

#Type 3 interaction p-value

[1]AUC 0-35% of the maximum rectangular (dips and spikes in VL); [2]AUC 36-40%; [3]AUC 41-55%; [4]AUC 56-100% (stable VL trajectories)

Conclusions: The degree of association between VCY and risk of clinical events varied across different AUC shapes, especially for AIDS/death. In particular, for a given difference in AUC, in people showing stable VL trajectories rather than periods of VL dips and spikes, VCY appear to better discriminate the risk. Strategies to maximize the chance of viral suppression should be considered for patients with suboptimal viral response even at low-level detectable viremia.

563 Monitoring and Switching of Antiretroviral Therapy in Sub-Saharan Africa

Andreas D. Haas[1]; Olivia Keiser[1]; François Dabis[2]; Mary-Ann Davies[3]; Rosalind M. Parkes-Ratanshi[4]; Steven J. Reynolds[5]; Kara Wools-Kaloustian[6]; Gilles Wandeler[1]; Matthias Egger[1]
IeDEA East, West and Southern Africa

[1]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland; [2]Université Bordeaux, Bordeaux, France; [3]University of Cape Town, Cape Town, South Africa; [4]Makerere University College of Health Sciences, Makerere, Uganda; [5]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US; [6]Indiana University, Indianapolis, IN, US

Background: Monitoring of antiretroviral combination therapy (ART) aims to maximize the durability of first-line ART regimens. Viral load monitoring is recommended but limited access to viral load tests in resource-limited settings means that decisions about switching to second-line ART are often based on clinical or immunological criteria. We examined monitoring of ART and switching to second-line regimens in sub-Saharan Africa.

Methods: We included adult treatment naïve HIV-1 infected patients starting ART in sub-Saharan Africa. Monitoring strategies were defined as routine virologic monitoring (>75 viral load tests per 100 person-years), routine immunological monitoring (>75 CD4 cell counts per 100 person-years), or clinical monitoring. Switching to second-line ART was defined as changing from an NNRTI-based regimen to a PI-based regimen and changing at least one NRTI. We calculated adjusted hazard ratios (aHR) and 95% confidence intervals (CI) from Cox regression models to identify predictors of switching.

Results: 421,518 patients from 38 ART programmes in 17 countries were followed for a total of 885,135 person-years of follow-up; 11,075 patients switched. Rates of switching ranged from 0.0 to 1.7 per 100 person-years in nine programmes with clinical monitoring, from 0.0 to 4.6 per 100 person-years in 21 programmes with immunological monitoring and from 1.1 to 4.2 per 100 person-years in eight programmes with virologic monitoring. Compared to clinical monitoring, switching was twice as common with virologic monitoring (aHR 2.30; 95% CI 1.44-3.68), but similar with immunological monitoring (aHR 0.99; 95% CI 0.85-1.16). Switching increased with viral load testing (Figure 1), was higher in urban than in rural sites, and higher in regional and University hospitals than in district hospitals or health centres. Effects were not explained by differences in patient characteristics. Among the patients with a confirmed immunological or virologic failure (n=25,300) only relatively few (16%) switched within two years after failure. The proportion of patients switching to second-line ART was lowest in programmes with clinical monitoring (7.9%-23.7%), and highest in patients with viral loads >10,000 copies/ml in CD4 monitoring sites (71.8%).

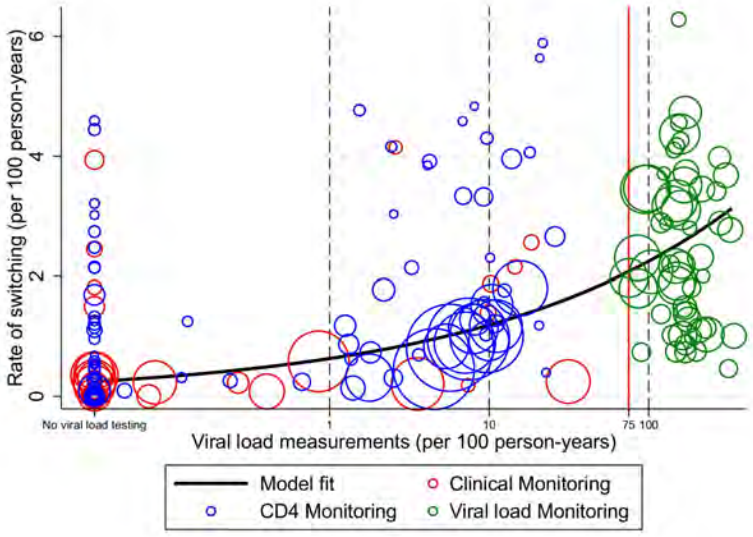


Figure 1: Bubble plot of rates of viral load testing and switching to second-line antiretroviral therapy according to monitoring strategy.

Rates were calculated by calendar year and site. The size of the circles is proportional to the number of person-years in the respective year and site.

Conclusions: Rates of switching to second line ART vary widely across treatment programmes in sub-Saharan Africa. Rates increase with viral load testing, but a sizable proportion of patients with documented virologic treatment failure are not switched to second-line ART.

564 Virological Factors Associated With Outcome of Dual MVC/RAL Therapy (ANRS-157 Trial)

Cathia Soulie[1]; Lambert Assoumou[2]; Melanie Darty[3]; Christophe Rodriguez[3]; Gilles Peytavin[4]; Marc-Antoine Valantin[5]; Dominique Costagliola[2]; Christine Katlama[5]; Vincent Calvez[1]; Anne-Genevieve Marcelin[1]
[1]Hôpital Pitié Salpêtrière, Paris, France; [2]INSERM/UPMC, Paris, France; [3]APHP Mondor, Creteil, France; [4]APHP Bichat, Paris, France; [5]Hôpital Saint-Louis, APHP, Université Paris Diderot, Paris, France

Background: ROCnRAL ANRS-157 was a single-arm study designed to evaluate a switch to a maraviroc (MVC) 300 mg bid plus raltegravir (RAL) 400 mg bid regimen in virologically suppressed patients with lipohypertrophy, and R5-tropic B or CRF02_AG HIV-1 subtype determined on DNA by Sanger sequencing. In these long-term antiretroviral experienced patients (n=44), the combo MVC/RAL lacks virological robustness despite a good treatment adherence, adequate respective plasma pharmacokinetics and benefit in lipid profile: 7 patients failed MVC/RAL therapy with 5 virological failures (VF) defined as two consecutive plasma viral load (pVL) > 50 cp/mL and 2 treatment discontinuations due to serious adverse events. The aim of this work was to investigate the factors associated with VF.

Methods: At baseline (BL), Ultra Deep Sequencing (UDS) of DNA gp120 V3 and integrase regions (454 Roche) and quantification of cellular HIV DNA were performed in PBMC. Viral tropism was interpreted using Geno2pheno algorithm (samples harboring >2% non-R5 variants were classified non-R5 viruses). Genotypic resistance mutations were evaluated according to the ANRS and IAS mutations list. Quantification of pVL was measured using an ultrasensitive assay (1 cp/mL). Tropism, BL ultrasensitive HIV RNA pVL, BL HIV DNA VL, subtype, age, ethnicity, transmission group, AIDS status, nadir CD4 and BL CD4 cell count, time since HIV diagnosis, duration of antiretroviral treatment, duration of suppressed viremia, pVL zenith, CD4/CD8 ratio, BL CD8 cell count were investigated as potential factors associated with VF.

Results: The proportion of patients with pVL < 1 cp/mL did not evolve overtime: 72%, 63%, 72%, 68%, 57%, 47%, 68% and 69% at BL, W4, W8, W12, W16, W20, W24 and end of the study respectively. Median BL cell associated DNA in PBMC was similar in patients with BL pVL< 1 and > 1 cp/mL (2.77 and 2.96 log_{10} copies/10^6 PBMCs, respectively). Among the 44 patients, 3 patients had minority X4-tropic viruses determined by UDS at BL and one of them presented VF. Some BL resistance mutations in integrase gene were detected by UDS at two positions: E138 and G140. None of studied factor was associated with VF.

Conclusions: Overall, the proportion of patients with a VL < 1 cp/mL was similar during all the follow-up, suggesting that VF is not related to a lack of efficacy of the MVC/RAL combination. Neither UDS, nor ultrasensitive viremia were an added value to predict VF in this context of MVC/RAL switch.

565 D-dimer Doesn't Return to Pre-HIV Levels After Therapy and Is Linked With HANA Events

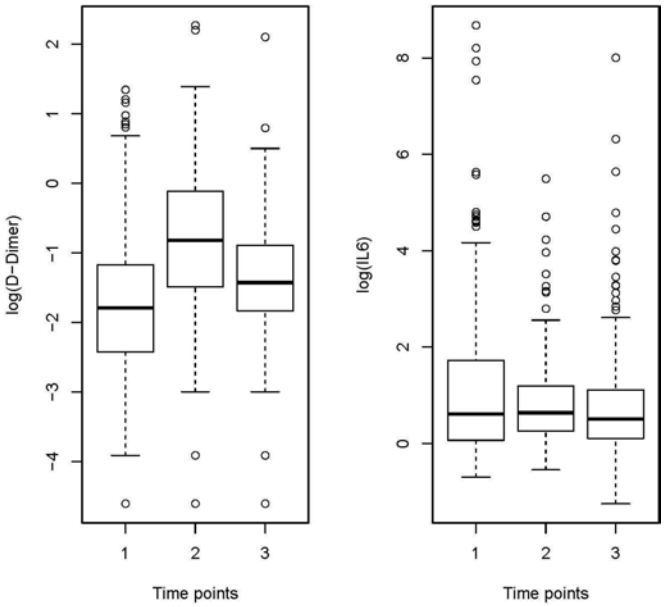
Matthew S. Freiberg[2]; Ionut Bebu[4]; Russell Tracy[3]; Jason F. Okulicz[1]; Anuradha Ganesan[1]; Adam Armstrong[5]; Thomas O'Bryan[1]; **Brian K. Agan**[1]
IDCRP HIV Working Group

[1]*Uniformed Services University of the Health Sciences, North Bethesda, MD, US;* [2]*Vanderbilt University Medical Center, Nashville, TN, US;* [3]*University of Vermont College of Medicine, Burlington, VT, US;* [4]*The George Washington University, Rockville, MD, US;* [5]*US Naval Medical Research Unit No. 6 Peru, Lima, Peru*

Background: Biomarkers of inflammation increase with HIV infection, and decline with therapy (ART). While it has been proposed that these markers fail to decline to levels that existed before HIV seroconversion (SC), this has never been directly demonstrated. Moreover, it is unknown whether this "residual" inflammation is associated with future HIV Associated Non AIDS (HANA) events.

Methods: We analyzed data/specimens on 249 HIV+ participants from the US Military HIV Natural History Study, a prospective, multicenter observational cohort of ~5500 active duty military personnel and beneficiaries living with HIV, who had available (1) cryogenically stored blood specimens at three defined timepoints (TP): TP1) pre-HIV SC (closest specimen at or prior to last negative HIV test), TP2) ≥6 months post-HIV SC but prior to ART initiation, and TP3) ≥6 months post-ART with HIV-1 RNA levels<50 copies/mL on two successive evaluations; (2) detailed medical history data including incident HANA events and (3) were free of liver disease, CVD, cancer, or steroid use. We used cox proportional hazards models to investigate the association between the changes in biomarker values (TP3-TP1, "residual inflammation") and HANA events while adjusting for confounders.

Results: Median ages were 27 (TP1); 30 (TP2); and 31 (TP3). At TP2 the population was 98% male, had median BP of 126/80 mmHg; AST/ALT of 30/28 IU/L; hemoglobin of 15 g/dL; total cholesterol, LDL, and triglyceride levels of 165, 107, and 139 mg/dL respectively; body mass index of 26. The median $CD4^+$ and duration of HIV infection were 361 cells/uL and 392 days, respectively. At TP3 median time on ART was 354 days. There were 27 incident HANA events during 1133 PY of f/u (median 3.74 yr). All comparisons between median D-dimer biomarker levels, but not IL-6 levels, for TP1,2 and 1,3 and 2,3 (figure), were significant p<0.001. "Residual inflammation" for D-dimer, but not IL-6, was significantly associated with incident HANA events (hazard ratio (HR)=1.43, 95% confidence interval 1.04-1.97, p=0.03; and HR=1.29, 95% CI 0.73-2.27, p=0.38), respectively.



Conclusions: After ART initiation and viral suppression, D-dimer remained elevated compared to pre-HIV SC levels in a cohort of healthy young adults. Residual D-dimer was also significantly associated with future HANA events. These data support the concept that successful ART alone does not eliminate inflammation associated with HIV infection, and may help explain the excess risk of non-AIDS diseases among those with HIV.

566 Virological Responses to Lamivudine and Emtricitabine in the Nationwide ATHENA Cohort

Casper Rokx[1]; Azzania Fibriani[1]; David A. van de Vijver[1]; Annelies Verbon[1]; Martin Schutten[1]; Luuk Gras[2]; Bart J. Rijnders[1]
On behalf of the Dutch HIV Monitoring Foundation

[1]*Erasmus University Medical Center, Rotterdam, Netherlands;* [2]*Academic Medical Center University of Amsterdam, Amsterdam, Netherlands*

Background: Lamivudine (3TC) and emtricitabine (FTC) are considered interchangeable in recommended combination antiretroviral therapies (cART) including tenofovir (TDF) with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or boosted protease inhibitor (PI). The evidence for equivalent efficacy of 3TC and FTC in cART is inconsistent and data from randomized clinical trials that directly compare FTC and 3TC are lacking. The purpose of this study was to evaluate the virological responses to 3TC and FTC in combination with TDF and efavirenz (EFV), nevirapine (NVP) or boosted PI in a nationwide cohort.

Methods: Observational cohort study on the AIDS Therapy Evaluation in the Netherlands (ATHENA) nationwide HIV cohort. Included were ART naive HIV-1 infected adults who initiated 3TC or FTC with TDF and either EFV or NVP or boosted PI between 2002 and 2012. Week 48 and week 240 virological failure to 3TC and FTC containing regimens were compared by multivariable adjusted logistic regression in on-treatment analysis. Time to 2 consecutive HIV-1 RNA <400 c/mL and time to virological failure after HIV-1 RNA <400 c/mL were compared by Cox proportional hazard models. Sensitivity analyses included intent to treat (ITT) analysis and propensity score adjusted models.

Results: During the 10 year study period, 6031 ART naive HIV1 infected adults initiated 3TC or FTC with TDF and either EFV (N=3878), NVP (N=862) or boosted PI (N=1291). Week 48 virological failure rates on 3TC compared to FTC were 10.8% and 3.6% with EFV (adjusted odds ratio (aOR):1.78, 95% confidence interval (95%CI):1.11-2.84), 27.0% and 11.0% with NVP (aOR: 2.09, 95%CI:1.25-3.52) and 5.3% and 4.7% with boosted PI (aOR: 1.44, 95%CI:0.51-4.03). Analysis by ITT and propensity score adjusted models gave similar results. The adjusted hazard-ratio on virological failure at week 240 using 3TC instead of FTC was 2.35 (95%CI:1.61-3.42) with EFV, 2.01 (95%CI:1.36-2.98) with NVP and 1.21 (95%CI:0.58-2.52) with boosted PI. The time to virological suppression <400 c/mL within 48 weeks and the time to virological failure after HIV-1 RNA <400 c/mL were not significantly influenced (P>0.05) by including either 3TC or FTC in EFV, NVP or boosted PI containing regimens.

Conclusions: The use of FTC as part of NNRTI containing regimens was associated with better virological responses. These findings are relevant for settings with extensive 3TC use and for including generic 3TC in cART.

567 Prevalence and Risk Factors of Multiple Micronutrient Deficiencies Pre- and Post-ART

Rupak Shivakoti[1]; Parul Christian[2]; Nikhil Gupte[1]; Cecilia Kanyama[3]; Sima Berendes[4]; Javier Lama[5]; Richard Semba[1]; Thomas Campbell[6]; Amita Gupta[1]
NWCS 319 and PEARLS Study Team

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]University of North Carolina Project–Malawi, Lilongwe, Malawi; [4]Malawi College of Medicine-Johns Hopkins University Research Project, Blantyre, Malawi; [5]Asociacion Civil Impacta Salud y Educacion, Lima, Peru; [6]University of Colorado School of Medicine, Aurora, CO, US

Background: Micronutrient deficiencies pose a special risk among immune suppressed HIV-infected adults resulting in an accelerated disease progression even when on antiretroviral therapy (ART). The objective of this study was to describe the prevalence and risk factors of multiple micronutrient deficiencies among ART-naïve HIV-infected adults from 9 countries and to test the hypothesis that micronutrient deficiencies are reduced 48 weeks post-ART initiation.

Methods: A random sub-cohort (n=270) stratified by country was selected from the ACTG PEARLS clinical trial (n=1571 ART-naïve, HIV-infected adults). We measured pre-ART serum concentrations of vitamins A, B_6, B_{12}, D (25-hydroxyvitamin), E, carotenoids, ferritin, soluble transferrin receptor, and selenium in 221-2 individuals with some losses of samples during export and processing. Prevalence and risk factors (using logistic regression) of single and multiple (≥3) micronutrient deficiencies were determined using defined serum concentration cutoffs. All micronutrients, except for vitamin B_6, vitamin B_{12}, and iron markers were also measured at 48 weeks post-ART. We assessed mean changes in micronutrient concentrations from pre-ART to week 48 post-ART using multivariable random effects models.

Results: Of 222 participants, 13.9%, 29.2%, 24.5% and 32.4% had 0, 1, 2 and multiple deficiencies, respectively. Pre-ART prevalence was the highest for single deficiencies of selenium (53.2%), vitamin D (42.4%), and B_6 (37.3%) with 12.1% having concurrent deficiencies of all three micronutrients. Independent risk factors for multiple micronutrient deficiencies were high inflammation and being from Brazil, India, Malawi, Peru, South Africa, Thailand and Zimbabwe relative to Haiti. In multivariable models adjusting for baseline micronutrient concentrations, gender, age, country, treatment arm, body mass index (BMI), CD4 count and viral load, mean concentrations of all the micronutrients (except vitamin D due to EFV treatment) increased (p<0.001) 48 weeks post-ART, but with minimal changes in deficiency status (**Table 1**).

Table 1: Change in micronutrient concentrations 48 weeks post-ART

		Baseline		48 weeks post-ART		
	N	Mean (SD)	Prevalence of deficiency % (95% CI)	Mean (SD)	Prevalence of Deficiency %(95% CI)	Mean Change at 48 weeks (95% CI)
Vitamin A (µmol/L)	222	1.66 (0.75)	17.1 (12.7-22.4)	1.85 (0.68)	8.1 (4.9-12.5)	0.21 (0.14-0.28)
Total Carotenoids (µmol/L)	221	1.25 (0.78)	25.0 (lowest quartile)	1.43 (0.80)	22.2 (16.9-28.2)	0.18 (0.09-0.27)
Vitamin D (ng/mL)	222	31.68 (11.30)	42.4 (36.2-48.8)	26.18 (10.90)	61.7 (55.0-68.1)	-6.28 (-7.58 to -4.98)
Vitamin E (µmol/L)	221	23.22 (6.37)	0.0	23.76 (6.71)	0.0	0.75 (-0.04-1.53)
Selenium (µg/L)	222	82.10 (28.83)	53.2 (46.8-59.5)	84.70 (27.56)	50.0 (43.2-56.8)	3.97 (2.15-5.79)

Conclusions: Single and multiple micronutrient deficiencies are common among HIV-infected adults pre-ART initiation but vary widely between countries. Importantly, despite changes in mean concentrations of micronutrients, prevalence of individual deficiencies remains largely unchanged after 48 weeks on ART. Our results suggest that ART alone is not sufficient to improve micronutrient deficiency.

568 Detection of HIV RNA and DNA in Anal Swabs of HIV Infected Men Having Sex With Men

Julian Storim[1]; **Jens Verheyen**[1]; Eva Wolff[1]; Lewin Eisele[1]; Jeremias Wohlschläger[2]; Peter-Michael Rath[1]; Evelyn Heintschel von Heinegg[1]; Dirk Schadendorf[1]; Stefan Esser[1]

[1]University Hospital Essen, University Duisburg-Essen, Essen, Germany; [2]University Hospital Essen, Essen, Germany

Background: Unprotected anal intercourse is high-risk behavior for acquiring HIV-infection. The transmission risk depends on plasma viral loads and concomitant sexual transmitted infections (STI). However, the effect of STI and antiretroviral therapy (ART) on the detection of HIV in the anal tract has not been scrutinized in detail.

Methods: 110 HIV-positive MSM, were recruited for proctological consultation at the outpatient center of the University Hospital Essen between November 2013 and February 2014. High-resolution anoscopy was performed and anal swabs were tested for *N.gonorrhoeae*(N.G.)-DNA, *C.trachomatis*(C.T.)-DNA, HPV genotypes, HI -RNA and integrated HIV DNA. Subsequently, these results were correlated with serological syphilis assays and HIV plasma viral loads (VL). Statistical analysis was performed using the Fisher's exact test.

Results: Anal condylomata acuminata were observed in 31 patients and bacterial STIs were diagnosed in 18 patients, of whom 7 patients had multiple bacterial STIs (N.G.: n=9, C.T.: n=12, T.P.: n=4). The majority of patients (89/110) carried at least one high-risk(HR)-HPV and 59 patients at least one low-risk(LR)-HPV. Bacterial STIs were associated with the presence of lymphocytes (p<0.01) and histiocytes (p<0.01) in cytological swabs. HIV-1 RNA was detected in 15 (14%) and integrated HIV DNA in 14 (13%) of 110 anal swabs. By comparing patients with ART and plasma HIV VL below the detection limit (n=88) with treatment-naïve (n=10) and patients with detectable viral loads with ART (n=12), the detection of anal HIV RNA and DNA were significantly correlated with HIV plasma VL above the detection limit (VL <40copies(c)/ml: 2/88 (RNA+) and 7/88 (DNA+) vs. VL >=40c/ml: 13/22 (RNA+) and 7/22 (DNA+), p<0.001 and p<0.01, respectively). Of note, also in ART-treated patients with plasma HIV-RNA <40c/ml anal HIV RNA (n=2) and DNA (n=7) could be detected. Coinfection with bacterial STI was diagnosed in 3 of these 7 ART-treated patients with detectable anal HIV DNA. All of the remaining four patients without bacterial STI and with HIV plasma RNA <40 (4/74) carried three or more HR-HPV (≤2 HR-HPV: 0/57 vs ≥3 HR-HPV: 4/17, p<0.01).

Conclusions: The detection of either HIV-1 RNA or DNA in anal swabs of MSM correlates with the HIV plasma VL and the coinfection with multiple HR-HPV. However, even anal swabs from ART-treated MSM with HIV plasma VL below the detection-limit could in part be tested positive for HIV-1 RNA and DNA.

WEDNESDAY, FEBRUARY 25, 2015

Session P-K3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

ART: Immunologic Response—The Good and The Bad

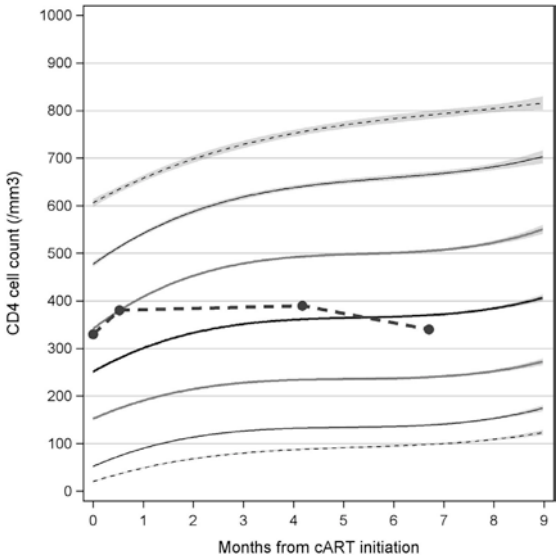
569 Reference Curves for CD4 Response to Antiretroviral Treatment in HIV-1–Infected Naïve Patients

Rodolphe Thiebaut
On behalf of the Standard Reference Distribution of CD4 Working Group in COHERE in EuroCoord
Bordeaux University, Bordeaux, France

Background: There is no consensus on how CD4+ T cell should increase in early response to combination antiretroviral treatment (cART). We provide references for CD4+ T cell increases following cART initiation in HIV-1 infected naïve patients with a good virological response at 6 months.

Methods: All individuals from the 33 cohorts participating in the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE), aged ≥ 18 years, who started cART for the first time between 1/1/2005 – 1/1/2010, with at least one available measure of CD4 count (in cells/μL) and HIV-1 RNA ≤50 copies/mL at 6 months (+-/ 3 months) after cART initiation were included. Unadjusted and adjusted reference curves and predictions were obtained through quantile regression.

Results: Observations from 28,992 patients were included in this analysis. Median (interquartile range IQR) CD4+ T cell count at treatment initiation was 249 (150; 336) cells/μL. The median observed CD4+ T cell counts at 6 months were 382 (256; 515). The figure shows the 5th, 10th, 25th, 50th, 75th, 90th, 95th percentiles of the overall population and the CD4 change of a specific individual (dots). A CD4+ T cell count increase of at least 100 cells/mL at 6 months is generally required in order that patients stay 'on track' (ie. on the same percentile as when they start), with slightly higher gains required to stay on track for those starting with CD4+ T cell counts in the higher percentiles. Hence, the median line demonstrates that patients who started cART at the median level of 251 cells/μL needed to have a CD4+ T cell count of 367 cells/μL at 6 months after cART initiation to remain on the median line. The two most influencing factors explaining the variation of CD4+ T cell count at 6 months were the AIDS stage at cART initiation and the baseline CD4+ T cell count. Predictions adjusted for factors influencing CD4+ T cell levels gave more precise individual predictions. For instance, a 25 years-old woman starting a PI-containing regimen before AIDS stage at 500 cells/μL with an increase to 600 cells/μL at 6 months is switching from the 51 percentile to the 46 percentile at 6 months after adjustment for her characteristics.



5th, 10th, 25th, 50th, 75th, 90th, 95th percentiles of the overall population CD4+ T cell change over months and trajectory for one individual (dots). COHERE.

Conclusions: Reference curves and predictions will help clinicians evaluate the immune response early after cART initiation leading to viral control, and may be useful to identify patients with poor CD4 count responses where greater monitoring or further interventions is needed.

570 Comparing Immunological Failure Definitions, Using Tanzanian National HIV Data

Fiona Vanobberghen[1]; Bonita K. Kilama[2]; Alison Wringe[1]; Angela Ramadhani[2]; Basia Zaba[1]; Donan Mmbando[3]; Jim Todd[1]
[1]London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]National AIDS Control Program, Dar es Salaam, United Republic of Tanzania; [3]Ministry of Health & Social Welfare, Dar es Salaam, United Republic of Tanzania

Background: Rates of first-line treatment failure and switches to second-line therapy are key indicators of national antiretroviral therapy (ART) programmes, but there is little consensus on the immunological failure (IF) criteria to be used in the absence of virological monitoring, which remains too expensive for most African national programmes.

Methods: Using routinely-collected data from the Tanzanian HIV programme, we compared IF rates using the criteria of WHO 2010, 2013 and Tanzania 2005, 2009 guidelines (with confirmatory CD4 counts). We included adults initiating ART in 2004-2011 with a pre-treatment CD4 count and ≥6 months of follow-up. For the WHO-2010 definition, we assessed sub- hazard ratios (SHRs) for IF and subsequent switch to second-line therapy, using competing risks methods to account for deaths.

Results: Among 121,308 adults, 6,108 (5.0%) to 19,380 (16.0%) persons experienced IF depending on the definition (Table). The cumulative probability of IF by 6 years ranged from 13.0% (12.5,13.4) under the WHO-2013 definition to 40.6% (39.8,41.5) under the WHO-2010-unconfirmed definition. Lower IF rates mean persons spending longer on first-line therapy and therefore higher death rates on first-line treatment, with a cumulative probability of death by 6 years of 5.3% (4.9,5.6) under the WHO-2013 definition versus 3.7% (3.4,3.9) under the WHO-2010-unconfirmed definition. IF predictors included ART initiation in dispensaries versus hospitals, being male, lower current weight and lower current CD4 count. Of 7,382 participants in the time-to-switch analysis, 416 (6%) switched, while 355 (5%) died before switching. Four years after IF, the cumulative probability of switching was 7.3% (6.6,8.0) and of death 6.8% (6.0,7.6). Those who immunologically-failed in dispensaries, health centres and government facilities were least likely to switch.

Definition	Description	Number (%) with IF	Number (%) died before IF	Cumulative probability of IF by 6 years	Cumulative probability of death by 6 years
WHO-2010	CD4 <50% of peak on-treatment value, <pre-treatment levels or CD4 <100 cells/mm^3; confirmed	8384 (6.9%)	2486 (2.0%)	19.1% (18.5,19.7)	5.1% (4.8,5.4)
WHO-2013	<pre-treatment levels or CD4 <100 cells/mm^3; confirmed	6798 (5.6%)	2521 (2.1%)	13.0% (12.5,13.4)	5.3% (4.9,5.6)
Tanzania-2005	CD4 <30% of peak on-treatment value or <pre-treatment levels; confirmed	9632 (7.9%)	2520 (2.1%)	30.9% (30.0,31.8)	4.9% (4.6,5.2)
Tanzania-2009	<50% of peak on-treatment value or <pre-treatment levels; confirmed	6108 (5.0%)	2591 (2.1%)	16.6% (16.0,17.3)	5.4% (5.1,5.7)
WHO-2010-unconfirmed	CD4 <50% of peak on-treatment value, <pre-treatment levels or CD4 <100 cells/mm^3; only the third component confirmed	19380 (16.0%)	2058 (1.7%)	40.6% (39.8,41.5)	3.7% (3.4,3.9)

Immunological failure definitions and rates.

Conclusions: IF rates and unmet need for second-line therapy are high in Tanzania, regardless of the IF definition. We recommend use of confirmatory CD4 counts to avoid unnecessary switching, despite the resulting slightly higher mortality. Clarification of the guidelines and virological monitoring, at least for persons with IF, is recommended. Lower-level government health facilities need more support to reduce treatment failure rates and improve uptake of second-line therapy, if the benefits of improved coverage through decentralisation are to be sustained.

571 Delaying Second-Line Therapy After First-Line Failure: Moderating Effect of CD4 Count

Julia K. Rohr[1]; Prudence Ive[2]; Rebecca H. Berhanu[3]; Kate Shearer[2]; Mhairi Maskew[2]; Lawrence Long[2]; Ian Sanne[2]; Matthew P. Fox[1]

[1]Boston University School of Public Health, Boston, MA, US; [2]University of Witswatersrand, Johannesburg, South Africa; [3]Right to Care, Johannesburg, South Africa

Background: Ideally patients who fail first line antiretroviral therapy (ART) are switched to second line quickly, yet logistical issues, clinician decisions and patient preferences make some delay in switching to second line ART common. Delays in switching to second line may be associated with poor outcomes on second line if resistance mutations develop or CD4 count declines substantially. This study explores the impact of delaying second line ART after first line failure on rates of virologic failure over multiple years on second line ART.

Methods: Observational cohort study using medical records from 9 clinics across South Africa, including patients with documented virologic failure on first line ART (2 consecutive viral load levels >1000 copies/mL) and at least one year of potential follow-up time after failure. Cox proportional hazards models analyzed the association between time to switch to second line (categorized) and virologic failure on second line ART. To account for patients who did not switch to second line, all patients were included in marginal structural models for death following first line failure. All models were stratified by peak CD4 count prior to failure to identify groups of patients for which delaying second line ART had the biggest impact on second line outcomes.

Results: 5,895 patients who failed first line ART were included in analysis. 37% never switched to second line. Among patients who switched, median time to switch after failure was 3.4 months (IQR: 1.1-8.7 months). Median follow-up time on second line was 1.4 years (IQR: 0.71-2.41 years). Among patients who did not switch, at one year after failure 48% had been lost from care, 5.7% died, and of those remaining in care 53% had evidence of re-suppression. In Cox models, delaying switch was associated with increased rates of virologic failure on second line for patients who had peak CD4 count prior to first line failure ≤ 100 cells/mm^3 (adjusted HR for switch in 3-6 months vs. 0-1.5 months = 2.13 (95% CI: 1.01, 4.47)). Marginal structural models, which adjusted for survivor bias, showed increased risk of death was associated with delaying switch to second line, especially among patients with low CD4 count prior to first line failure (adjusted HR for switch in 6-12 months vs. 0-1.5 months = 1.49 (95% CI: 0.91, 2.42)) (Table).

Table. Marginal structural model results showing hazards of death after first line treatment failure.

		Peak CD4 ≤ 100 cells/mm^3			Peak CD4 >100 cells/mm^3		
Variables		HR	HR 95% LCL	HR 95% UCL	HR	HR 95% LCL	HR 95% UCL
Time to switch to second line ART	No switch	1.55	0.95	2.53	1.20	0.82	1.76
	0-1.5 months	Ref			Ref		
	1.5-3 months	1.39	0.85	2.27	0.93	0.64	1.34
	3-6 months	1.31	0.81	2.15	0.98	0.68	1.42
	6-12 months	1.49	0.91	2.42	1.22	0.82	1.79
	>12 months	1.52	0.94	2.46	1.11	0.77	1.62
Gender	Female	Ref			Ref		
	Male	0.81	0.46	1.42	1.37	0.92	2.02
Age	18-25	0.92	0.37	2.29	0.87	0.31	2.38
	25-30	0.76	0.34	1.68	1.22	0.64	2.33
	30-35	Ref			Ref		
	35-40	0.58	0.23	1.46	1.26	0.73	2.16
	40-45	0.39	0.15	0.99	1.02	0.53	1.97
	45-50	0.65	0.23	1.84	0.91	0.40	2.08
	50-55	1.06	0.35	3.22	1.75	0.70	4.37
	55+	0.65	0.19	2.24	1.53	0.55	4.25
Failing viral load	1000-9999	0.39	0.19	0.80	0.51	0.31	0.84
	10,000-59,999	0.82	0.42	1.63	0.57	0.35	0.95
	60,000+	Ref			Ref		
CD4 count at failure	0-49				2.46	1.20	5.04
	50-99				Ref		
	100-250				0.72	0.41	1.28
	>250				0.42	0.20	0.85

Conclusions: Even small delays in switch to second line ART was associated with increased virologic failure and increased death on second line among patients with low CD4 counts on first line.

572 Rapid Progression Hinders the Recovery of CD4 + T Cells Following Initiation of cART

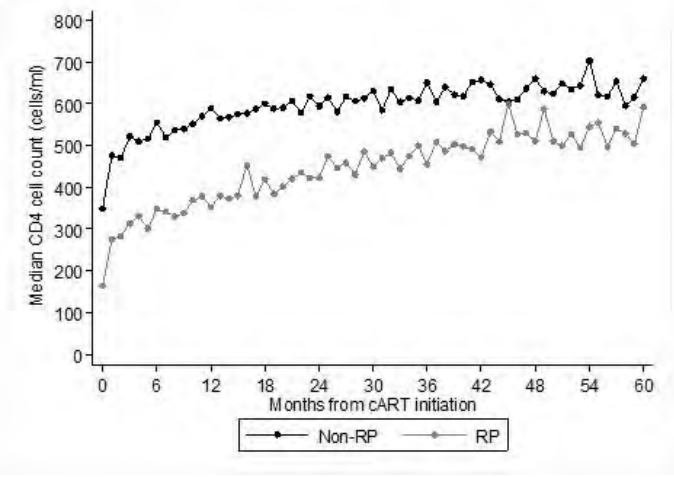
Inma Jarrin
On behalf of the CASCADE Collaboration within EUROCOORD
Instituto de Salud Carlos III, Madrid, Spain

Background: We aimed to compare trends in CD4+ T-cell recovery after combination antiretroviral therapy (cART) initiation and proportion of patients achieving optimal CD4+ T-cell restoration (counts ≥500 cells/μl) after 12, 36 and 60 months of viral suppression between rapid (RP) and non-rapid progressors (non-RP).

Methods: We included HIV-1 seroconverters (SC) from CASCADE who initiated cART from naïve and achieved viral suppression within the first 6 months. Individuals were classified as RP if they experienced ≥1 CD4+<200 cells/μl within 12 months from SC before cART initiation, non-RP if not. We used piecewise linear mixed-models (slopes changes at months 1 and 18) to model trends in CD4+ T-cell counts and logistic regression to calculate Odds Ratios for optimal restoration. Models were adjusted for sex, risk group, geographical origin, age and HIV-RNA at cART initiation. To compare RP and non-RP with the same baseline CD4+ T-cell count, we applied a post-estimation adjustment procedure to the results of the multivariate linear mixed model and we also fitted multivariate logistic regression models which included an adjustment for CD4+ T-cell count at cART (<100, 100-199, ≥200) initiation.

Results: Of 4,197 individuals, 307 (7.3%) were classified as RP. Median CD4+ T-cell count profiles are shown in Figure 1. Comparison of RP and non-RP with the same baseline CD4+ T-cell count showed that RP experienced a faster CD4+ T-cell increase than non-RP in the first month [difference (95% CI) in mean CD4+ T-cell increase/month (square root scale): 1.87 (1.65; 2.10)], slightly slower increases in months 1-18 [-0.05 (-0.06; -0.03)] and no significant differences in 18-60 [0.001 (-0.010; 0.012)]. Percentage of patients achieving an optimal restoration was significantly lower in RP than non-RP at months 12 (29.0 versus 64.2%) and 36 (46.3% versus 73.2%) but not at month 60 (70.2% versus 72.3%), differences that disappeared after comparing patients with the same CD4+ T-cell count at start of cART: OR (95% CI) 0.79 (0.54; 1.15), 0.79 (0.34; 1.83) and 1.61 (0.58; 4.45) at months 12, 36 and 60, respectively.

Figure 1. Observed CD4+ T-cell counts in RP and non-RP



Conclusions: Although RP experience faster initial increases of CD4+ T-cell counts that non-RP on suppressive therapy, they are less likely to achieve optimal CD4+ T-cell restoration during the first 36 months after cART, mainly due to their lower CD4+ T-cell counts at cART initiation.

573 Increase in CD4 Counts at Presentation to ART Care Among Urban HIV Clinics in Uganda

ELIZABETH K. NALINTYA[1]; Agnes N. Kiragga[1]; Edison Katunguka[2]; Henry W. Nabeta[1]; Joanita Kigozi[1]; Yukari Manabe[4]; David R. Boulware[2]; Jon Kaplan[3]; David B. Meya[1]
[1]Infectious Diseases Institute, Kampala Uganda, Kampala, Uganda; [2]University of Minnesota, Minneapolis, MN, US; [3]CDC Center for Global Health, Division of Global AIDS/HIV, Atlanta, GA, US; [4]Johns Hopkins University, Baltimore, MD, US

Background: In resource-limited settings, the increased availability of HIV testing services, scale-up of antiretroviral therapy (ART), and revised ART initiation guidelines has led to increased accessibility to HIV care. We hypothesized that HIV-infected persons are seeking care earlier compared with the era of initial ART roll-out in sub-Saharan Africa. We investigated the median CD4 count at presentation to care and the proportion presenting with CD4 counts ≤100 cells/μL from 2005 to 2013.

Methods: Data on CD4 counts at enrollment in care were obtained from 8 urban municipal clinics in Kampala District (KCCA clinics) where HIV care services are supported by PEPFAR and the Infectious Disease Institute (IDI) in Uganda. Multiple linear regression examined associations with CD4 count by year. Results were adjusted for clinic site with robust standard errors to account for clustering.

Results: A total of 59327 HIV-infected persons were registered for care in the KCCA clinics in 2005 – 2013, of whom 21895 (36.9%) had documented CD4 results at entry into care. Of these, 73% were women; median age was 32 years (Interquartile range: 26, 39). The median CD4 count increased steadily through the study period from 168 cells/μL in 2005 to 263 cells/μL in 2013 (Figure 1). Overall, there was a 20% reduction in the proportion of people presenting with CD4 <100 cells/μL from 24.7% in 2005 to 20.2% in 2013 (P<0.001). During the study period, a greater proportion of men (35.6%) presented with CD4<100 than women (24.3%, P<0.001). After adjusting for age, gender, and clinic site, the mean increase in CD4 count at presentation per year was 6.0 cells/μL per year (95%CI: 1.0 to 12.0 cells/μL per year).

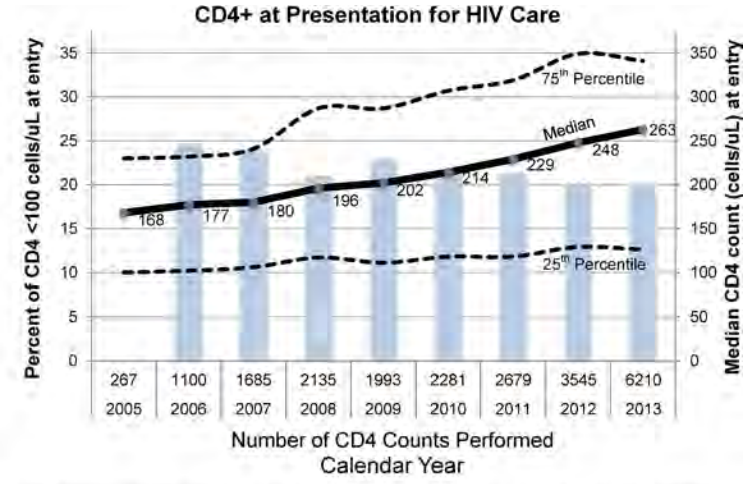


Figure displays the median (IQR) of CD4 counts at entry into HIV care (line graph) and the proportion of presenting CD4<100 cells/μL (bar graph) with the number of CD4 counts

Conclusions: For persons in whom CD4 counts were available, there has been a gradual, sustained increase in median CD4 counts at presentation to HIV care in Kampala, Uganda from 2005 to 2013; however, a substantial proportion (20%) still present with advanced AIDS and CD4<100. In light of the current ART start guidelines, more effort is required to ensure eligible patients enroll into care.

574 Implications of Poor CD4 Recovery During HIV Suppressive ART in Sub-Saharan Africa

Marieke E. de Pundert[1]; Tamara Sonia Boender[1]; Raph L. Hamers[1]; Kim Sigaloff[1]; Cissy M. Kityo[2]; Alani S. Akanmu[3]; Maureen Wellington[4]; Tobias F. Rinke de Wit[1]; Pascale Ondoa[1]
Pan African Studies to Evaluate Resistance (PASER) studygroup

[1]Amsterdam Institute for Global Health and Development, Brasschaat, Belgium; [2]Joint Clinical Research Centre Kampala, Kampala, Uganda; [3]Lagos University Teaching Hospital, Lagos, Nigeria; [4]Newlands Clinic, Harare, Zimbabwe

Background: Achieving undetectable plasma viral load (VL) on antiretroviral therapy (ART) is not always accompanied by the recovery of CD4 count. This study evaluates determinants, clinical outcomes and time trends of poor CD4 recovery in patients receiving suppressive ART in the Pan-African Studies to Evaluate Resistance Monitoring (PASER-M) cohort.

Methods: In 2585 patients with pre-ART CD4<200 cells/μL VL<50 RNA c/mL, poor CD4 recovery was defined as CD4<200 or gain <100 cells/μL at month 12, and CD4<350 or gain <100 cells/μL at month 24. Determinants were assessed using logistic regression. Clinical outcome beyond 12 months was assessed using logistic regression and Kaplan-Meier analysis. Positive predictive value (PPV) was used to determine the (change in) predictive capacity of CD4 count to identify virological failure using WHO-recommended immunological criteria, at month 12, 24 and 36.

Results: At month 12, risk factors were older age ≥40 (OR=2.38, 95%CI1.45-3.90), nevirapine (OR=1.52, 95% CI1.05-2.22), and lower pre-ART CD4 count per 50 cells/μL stage (OR=0.65, 95%CI 0.59-0.72). At month 24, these factors were male sex (OR=1.61, 95%CI1.12-2.31), AIDS at ART initiation (OR=0.46, CI 95%0.25-0.84), and poor CD4 recovery at month 12 (OR=9.45, CI95% 6.33-14.10). Determinants of persistent poor CD4 recovery, at both month 12 and 24, were older age (OR=3.90, CI95%1.45-10.49), lower pre-ART CD4 count (OR=0.74, CI95%0.63-0.87) and AIDS at ART initiation (OR=0.36, CI95%0.15-0.89). Poor CD4 recovery at month 12 was associated with a significantly higher risk of HIV-related mortality between month 12 and 24 (OR=3.78, CI95%1.26-11.41). Proportions of poor CD4 recovery remained stable during the follow-up period (between 12.8 and 19.8%), with persistently low predictive capacity of WHO-defined immunological criteria on virological failure throughout the observation period (PPV= 16%, 34% and 37% at month 12, 24 and 36).

Conclusions: Early ART initiation prevents the occurrence of adverse clinical outcomes in the face of undetectable VL. Proportions of poor CD4 recovery do not decrease over time, suggesting that risk factors for poor CD4 recovery that were not present at baseline may emerge in the course of the treatment. Routine VL monitoring is warranted to reliably identify virological failure during early and long-term response to ART. CD4 count might carry important information on clinical outcome during suppressive ART.

575 Better CD4/CD8 Restoration in First-Line HIV-Infected CMV-Seronegative Patients

Isabelle Poizot-Martin[1]; Clotilde Allavena[2]; Claudine Duvivier[3]; Carla E. Cano[1]; Francine Guillouet de Salvador[4]; David Rey[5]; Lise Cuzin[6]; Antoine Cheret[7]; Bruno Hoen[8]
On behalf of the Dat'AIDS Group

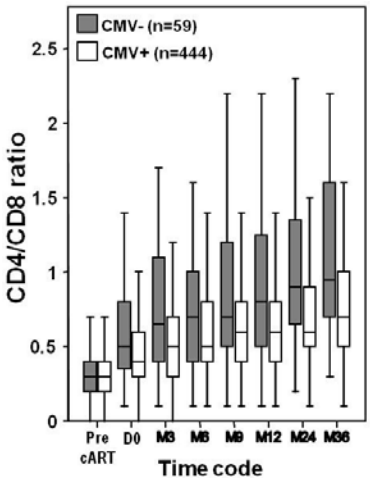
[1]Aix-Marseille Univ, APHM Hôpital Sainte-Marguerite, Marseille, France; [2]CHU Hotel Dieu, Nantes, France; [3]APHP–Hopital Necker–Université Paris Descartes–IHU Imagine, Paris, France; [4]CHU Archet 1, Nice, France; [5]Hôpitaux Universitaires Strasbourg, Strasbourg, France; [6]Regional Coordination for HIV, Toulouse, France; [7]Hospital Tourcoing, Tourcoing, France; [8]University Medical Center of Guadeloupe, Guadeloupe, France; [9]The Dat'AIDS Group, Nice, France

Background: CMV-infection is highly prevalent among HIV-infected patients. We investigated its impact on immune reconstitution in HIV-infected patients receiving their first cART.

Methods: From the French multicenter Dat'AIDS cohort, we selected patients who initiated a first cART between 2002 and 2009, maintained an undetectable plasma viral load (pVL) for at least 12 months with the same cART regimen and had a known CMV serostatus. T-cell immunophenotyping was performed before cART initiation (pre-cART), at the first undetectable pVL (D0), and every 6 months during 3 yrs.

Results: 5,688 patients initiated a first cART during the study period, 503 of whom fulfilled the selection criteria (74% male, median age 43 yrs, 15.5% CDC stage C), distributed in 444(88.3%) CMV+ and 69 CMV -. Median CD4 nadir (222/mm3) and exposure to first-line cART (32.3 months) were not different by CMV status. Chronic hepatitis C (HCV-PCR+) was equally prevalent (5.2%) in CMV+ and CMV- patients. Median follow-up was shorter in CMV+(1[0.2;3.4] yrs) than in CMV- (3.4[0.3;8.4]yrs, p<0.05). Both groups had similar median pre-cART CD4 (250[162;319]/mm3) and pre-cART CD8 (772[530;1123]/mm3) values. After 3 yrs, CD4 reconstitution was comparable between the groups, while absolute and differential CD8 cell counts were higher in CMV+ (816[583;1017] vs. 615[383;849]/mm3 in CMV-, p<0.001). Bivariate analysis revealed a negative correlation between CMV+

serology and CD4/CD8 ratio from D0 of HIV suppression (Figure 1: box plot & Pearson's R). Linear regression analyses using CD8 or CD4/CD8 ratio as dependent variables, and CMV serology, duration of HIV exposure, CD4 nadir and cART regimen as independent variables, confirmed a negative correlation between CMV+ serology and CD4/CD8 ratio after 1, 2 and 3 yrs of cART initiation (p<0.05, <0.001 and <0.001, respectively).



	R	p
Pre cART	ns	
D0	-0.18	0.02
M3	-0.2	<.001
M6	-0.13	<.001
M9	-0.16	<.001
M12	-0.18	<.001
M24	-0.2	<.005
M36	-0.25	0.015

Conclusions: CMV+ serostatus is associated with poorer immunological response to cART initiation compared to CMV- serostatus despite efficient control of HIV replication. Thus, CMV serological status should be taken into account when measuring the effectiveness of antiretroviral therapy on immune restoration.

576 CD4 Response in Treatment-Naïve HIV-2–Infected Patients: The IeDEA West Africa Cohort

Eric Balestre[1]; Koumavi K. Ekouevi[2]; Boris Tchounga[2]; Serge P. Eholié[3]; Eugène Messou[4]; Adrien Sawadogo[5]; Rodolphe Thiebaut[1]; Margaret T. May[6]; Jonathan A. Sterne[6]; François Dabis[1]

[1]Univ Bordeaux, ISPED, Centre Inserm U897-Epidemiologie-Biostatistique, Bordeaux, France; [2]Programme PAC-CI, Centre Hospitalier Universitaire de Treichville, Abidjan, Côte d'Ivoire; [3]Service de Maladies Infectieuses et Tropicales, Centre Hospitalier Universitaire de Treichville, Abidjan, Côte d'Ivoire; [4]Centre de Prise en Charge de Recherche et de Formation, Hôpital Yopougon Attié, Abidjan, Côte d'Ivoire; [5]Institut Supérieur des Sciences de la Santé, Université Polytechnique de Bobo-Dioulasso, Bobo-Dioulasso, Burkina Faso; [6]School of Social and Community Medicine, Bristol University, Bristol, United Kingdom

Background: Response to antiretroviral therapy (ART) among individuals infected with human immunodeficiency virus type 2 (HIV-2) is poorly understood. We compared the immunological response among patients treated with three nucleoside reverse transcriptase inhibitors (NRTIs) and with protease inhibitor (PI) based regimens.

Methods: This prospective cohort study enrolled HIV-2-infected patients within the International epidemiological Database to Evaluate AIDS (IeDEA) collaboration in West Africa. Patients aged >17 years at ART initiation and with an HIV-2 infection confirmed by two or three rapid HIV tests were eligible. Only those patients who initiated ART with three NRTIS or a PI-based regimen were included. The treatment effects on CD4 count were estimated with linear mixed models over 24 months. To address possible informative dropout we performed a sensitivity analysis restricted to patients remaining in care.

Results: Of 422 HIV-2-infected patients, 389 (92.2%) were treated with a PI-based regimen and 33 (7.8%) with three NRTIs. Treatment groups were comparable with regard to gender (54.5% female), median age at ART initiation (45.3 years; interquartile range [IQR] 38.3-51.8), clinical stage (17.3% at CDC stage C or WHO stage IV) and median length of follow-up (22.5 months; 4.3-45.6). Baseline median CD4 count was 164 cells/μl (76-250) in the PI-based regimen group compared to 192 cells/μl (114-308) in the three NRTIs regimen group (p=0.07). Twenty-four months after starting ART there were 17 deaths in total (4.0%, p=1.00) and 33% of patients were lost to follow-up (p=0.98). CD4 count response to ART was significantly higher for patients with a lower initial CD4 count (p=0.047) and for women (p=0.016). CD4 count recovery at 6 months was lower for patients treated with three NRTIs than for those treated with a PI (-53 cells/μl; 95% CI -105;-1, p=0.046). This difference was no longer significant at 12 months (-43 cells/μl; -102;17, p=0.16) and 24 months (+4 cells/μl; -81;89, p=0.92). The results of the sensitivity analysis restricted to patients remaining in care were similar.

Conclusions: In this observational study using African data, PI-containing regimens had similar immunological response than triple NRTI combinations at 12 months. A randomized clinical trial is still required to determine the best initial regimen for treating HIV-2 infection.

WEDNESDAY, FEBRUARY 25, 2015

Session P-K4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

ART: Mortality

577 Mortality and Retention After 12 Months in a Cohort of Patients Initiated With the New WHO Recommendations in Uganda

John Ssali; Juan Gonzalez Perez; Jonathan Ikapule; Lydia Buzaalirwa; Kate Ssamula; Augustine Lubanga; Sulaiman Kawooya; Monday Busuulwa; Penninah Lutung Amor; **Michael Wohlfeiler**

AIDS Healthcare Foundation, Kampala, Uganda

Background: The 2013 WHO guidelines recommend to start ART in all individuals with CD count 500 cells/mm^3 or less regardless clinical stage. Evidence for clinical benefit of initiation between 350-500 cells is limited and relies mainly in observational studies from high income countries. Concerns about high risk of defaulting in those patients have also been raised. Here we present data on retention and mortality after 12 months on treatment from a cohort of patients initiated on ART with less than 500 CD4 cells in Uganda as part of a pilot on early ART initiation.

Methods: Data from adult patients started on ART between December 2012 and August 2014 in four facilities ran by AIDS Healthcare Foundation in Uganda was included and stratified in three categories according to their baseline CD4 count: 0-200, 201-350 and 351-500 cells. Kaplan Meier estimates of mortality and retention after 12 months on ART were calculated for each group.

Results: Of 5601 patients, 56 % were women, median age was 34 years and 35% had a CD4 baseline between 351-500 cells. During 3737 person-years follow up, there were 128 deaths. Mortality rates were 79.7 deaths per 1000 person-years (95% CI 64.4- 98.7) in the CD4 0-200 category, 22 deaths per 1000 person-years (95% CI 15.2-31.9) in the CD4 201-350 and 11.3 (95% CI 6.9-18.5) in the CD4 351-500. Differences in mortality between the last two groups were statistically significant (log rank test: p=0.03) Retention after 12 months on ART was 78.7%, 86.7% and 86.9% respectively for the CD4 0-200, 201-350 and 351-500 categories

Conclusions: Our analysis found decreased mortality in the first year of ART in patients started with a baseline CD4 above 350 cells compared with those initiated with CD4 201-350 cells suggesting that the new WHO recommendations can also have individual clinical benefit in resource limited settings. Retention at 12 months in both groups was similar and above 85%.

578 Effect of ART on Mortality Generalized to Newly HIV-Diagnosed Persons in the USA

Catherine R. Lesko[1]; Stephen R. Cole[1]; H. Irene Hall[3]; Michael J. Mugavero[2]

[1]University of North Carolina, Chapel Hill, NC, US; [2]University of Alabama at Birmingham, Birmingham, AL, US; [3]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: Existing estimates of the effect of ART on survival have come from interval and clinical cohorts that differ on patient demographic and clinical characteristics from recently HIV-diagnosed persons in the United States (US) (the target population). If the effect of ART varies with respect to these same patient characteristics, then the magnitude of existing estimates of the effect of ART on survival may not be directly generalizable to the recently diagnosed US population.

Methods: Patients (n=12,547) initiating HIV care in eight academic medical centers in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) after January 1, 1998 were followed until death from any cause, administrative censoring at 5 years after therapy initiation or the end of follow up on December 31, 2011. The target population was persons diagnosed with HIV in the US between 2009 and 2011, which was provided by the Centers for Disease Control and Prevention from national HIV surveillance data. We estimated 5-year mortality from the complement of standardized Kaplan-Meier survival functions and described the relative reduction in the hazard of mortality due to ART using a marginal structural Cox proportional hazards model. Bias due to confounding and drop out were controlled using inverse probability weights for treatment and drop out. The effect of ART was estimated within subgroups defined by a priori selected patient demographic and clinical characteristics using stratified analyses. We standardized our final estimate of the effect of ART on survival to the recently HIV-diagnosed population using inverse probability weights for generalizability.

Results: The hazard of all-cause mortality among ART initiators was 0.33 (95% CI: 0.25, 0.43) times the hazard among non-initiators. The protective effect of ART was stronger among patients with no history of injection drug use, lower CD4 cell count at baseline, no prior AIDS diagnosis, and non-Hispanic white race/ethnicity. Although conditions were present that might preclude generalizability of the study estimate, the HR among persons recently HIV-diagnosed in the US was similar (HR=0.32, 95% CI: 0.23, 0.45).

Conclusions: We demonstrate the use of formal methods for generalizing an estimate of effect from one cohort to a different target population. The similarity of the results in both the CNICS cohort and the recently HIV-diagnosed provides reassuring evidence for the external validity of research conducted in the CNICS.

579 Association of CD4:CD8 With Cause-Specific Mortality in Patients on Long-Term ART

Margaret T. May[1]; Adam Trickey[1]; Dominique Costagliola[6]; Peter Reiss[4]; Santiago Moreno[5]; John Gill[3]; Colette Smith[2]; Suzanne M. Ingle[1]; Jonathan A. Sterne[1]
On behalf of the Antiretroviral Therapy Cohort Collaboration (ART-CC)

[1]University of Bristol, Bristol, United Kingdom; [2]University College London, London, United Kingdom; [3]University of Calgary, Calgary, Canada; [4]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [5]Hospital Ramón y Cajal, Madrid, Spain; [6]UMR S 1136, Inserm et Sorbonne Universités, Université Pierre et Marie Curie, Paris, France

Background: Patients with advanced HIV disease have low CD4:CD8 ratios. These improve with effective ART, but increases in ratios are largely due to higher CD4 counts with persistently high CD8 counts limiting further normalization of the ratio, even after 5 years of ART. Low CD4:CD8 ratios are associated with mortality in elderly HIV-negative people, and have been suggested to reflect HIV-related immune senescence.

Methods: Adult patients from 12 European and North American cohorts contributing to the Antiretroviral Therapy Cohort Collaboration were followed for cause-specific mortality from 5 years after starting ART. Baseline CD4 and CD8 counts were those nearest to and within 3 months of 5 years after ART start. We used Cox models, stratified by cohort, to estimate hazard ratios (HR) for subsequent all-cause, AIDS-related, and non-AIDS related (excluding unnatural deaths) mortality comparing patients with CD4:CD8 ratio ≥0.5 and < 0.5 (reference group), stratified by CD4 count (< 350, ≥ 350, and ≥ 500 cells/mm^3). We fitted models that were unadjusted; adjusted for CD4; and additionally adjusted for sex, age, IDU transmission group, ART start year, AIDS and viral suppression at 5 years.

Results: During 98,438 person-years 902/20,464 patients died. Cause of death was available in 63% of deaths. Median (inter-quartile range) CD4:CD8 ratio 5 years after ART start was 0.61 (0.40, 0.89) and 0.41 (0.23, 0.72) in those who survived and died, respectively (0.23 (0.09, 0.41) for AIDS deaths; 0.45 (0.27, 0.77) for non-AIDS deaths). At 5 years, 9698 (47%) patients had CD4:CD8 ratio >1. Lower CD4:CD8 ratios were associated with mortality in all groups, but these associations were completely attenuated after adjustment for CD4 in those with CD4 counts <350 cells/mm^3. By contrast, the adjusted HR (95% CI) in patients with CD4 ≥350 cells/mm^3 was 0.68 (0.56, 0.84). In patients with CD4 ≥500 cells/mm^3 the adjusted mortality HR (95% CI) for CD4:CD8 ≥ 0.5 (v. < 0.5) was 0.71 (0.32, 1.56). In patients with CD4 ≥ 350 cells/mm^3 low CD4:CD8 was associated with both non-AIDS and AIDS-related deaths, but confidence intervals were wide.

Table: Association of CD4:CD8 ratio with mortality stratified by CD4 count

5 year CD4 count cells/mm^3	Patients (deaths)	Mortality HR (95% CI) for CD4:CD8 ratio ≥ 0.5 versus < 0.5 Unadjusted	Adjusted for CD4	Fully adjusted*
		All-cause mortality		
CD4<350	5015 (424)	0.65 (0.50, 0.85)	0.93 (0.70, 1.22)	1.08 (0.81, 1.44)
CD4≥350	15448 (478)	0.56 (0.47, 0.67)	0.58 (0.47, 0.70)	0.68 (0.56, 0.84)
		AIDS-related deaths		
CD4<350	4689 (97)	0.39 (0.20, 0.76)	1.00 (0.49, 2.02)	1.35 (0.66, 2.79)
CD4≥350	15002 (32)	0.41 (0.20, 0.82)	0.41 (0.20, 0.90)	0.51 (0.23, 1.13)
		Non-AIDS-related deaths		
CD4<350	4748 (156)	0.83 (0.56, 1.22)	1.07 (0.71, 1.61)	1.32 (0.86, 2.02)
CD4≥350	15178 (208)	0.57 (0.43, 0.76)	0.56 (0.41, 0.76)	0.70 (0.51, 0.96)

*Adjusted for CD4, Sex, Age, IDU, AIDS, Viral suppression, HAART start year

Conclusions: CD4:CD8 ratios may be useful for monitoring mortality risk in patients on long-term ART.

580 Outcomes of First ART in Latino Populations in North America and Latin America

Carina T. Cesar[1]; Mark J. Giganti[2]; Bryan E. Shepherd[2]; Richard Moore[3]; Keri N. Althoff[3]; Sonia Napravnik[4]; Angel M. Mayor[5]; Catherine Mc Gowan[2]; Pedro E. Cahn[1]

[1]Fundacion Huesped, Buenos Aires, Argentina; [2]Vanderbilt University, Nashville, TN, US; [3]Johns Hopkins University, Baltimore, MD, US; [4]University of North Carolina, Chapel Hill, NC, US; [5]Retrovirus Research Center, Bayamon, US

Background: HIV outcomes and response to ART may be influenced by viral, host, and environmental factors, and differences in health care setting. The goal of this project was to compare rates of ART failure and mortality between HIV-infected adults in Latin America to those with Latino ethnicity from North America.

Methods: ART-naive HIV-infected adults who initiated first ART from 2000 to 2012 at Caribbean, Central and South American Network for HIV (CCASAnet) sites in Argentina, Chile, Honduras, Mexico and Peru were compared to those with Latino ethnicity from North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) sites. Patients were defined as Latino if they had Latin American origin or ancestry by self-report. Cox proportional hazards models compared all-cause mortality between cohorts, accounting for sex, age, AIDS at ART start, nadir CD4, calendar year, and regimen class. Prevalence of VL >400 was compared by negative binomial regression.

Results: 6223 ART initiators from CCASAnet and 3250 from NA-ACCORD met inclusion criteria; median follow-up was 3.9 years (interquartile range [IQR] 1.6-6.9) and 2.7 (IQR 1.0-5.5), respectively. ART initiators in CCASAnet were younger (median 35 vs. 37 years), more likely to be female (24% vs. 20%), less likely to have acquired HIV through injection drug use (0.5% vs. 13%), more likely to have AIDS prior to ART start (34% vs. 21%), and more immunosuppressed (median nadir CD4 of 139 vs. 208) compared with NA-ACCORD ART initiators (p<0.01 for all). Nearly 90% of patients started a non-nucleoside reverse transcriptase inhibitor-based regimen in CCASAnet compared to 45% in NA-ACCORD (p<0.01). The most common initial nucleoside backbone was ZDV/3TC in CCASAnet and TDF/FTC in NA-ACCORD (68% and 56%, respectively). Subjects in CCASAnet had a higher adjusted hazard ratio for mortality (1.25, 95% confidence interval [CI]: 1.02-1.54). VL was measured less frequently in CCASAnet than NA-ACCORD (median 1.8 vs. 3.27 measures per person per year), and the percentage of VL measurements that were detectable was higher in CCASAnet (adjusted prevalence ratio=1.34, 95%CI: 1.21-1.50).

Funded by NIH 2-U01-AI069923 & U01-AI069918

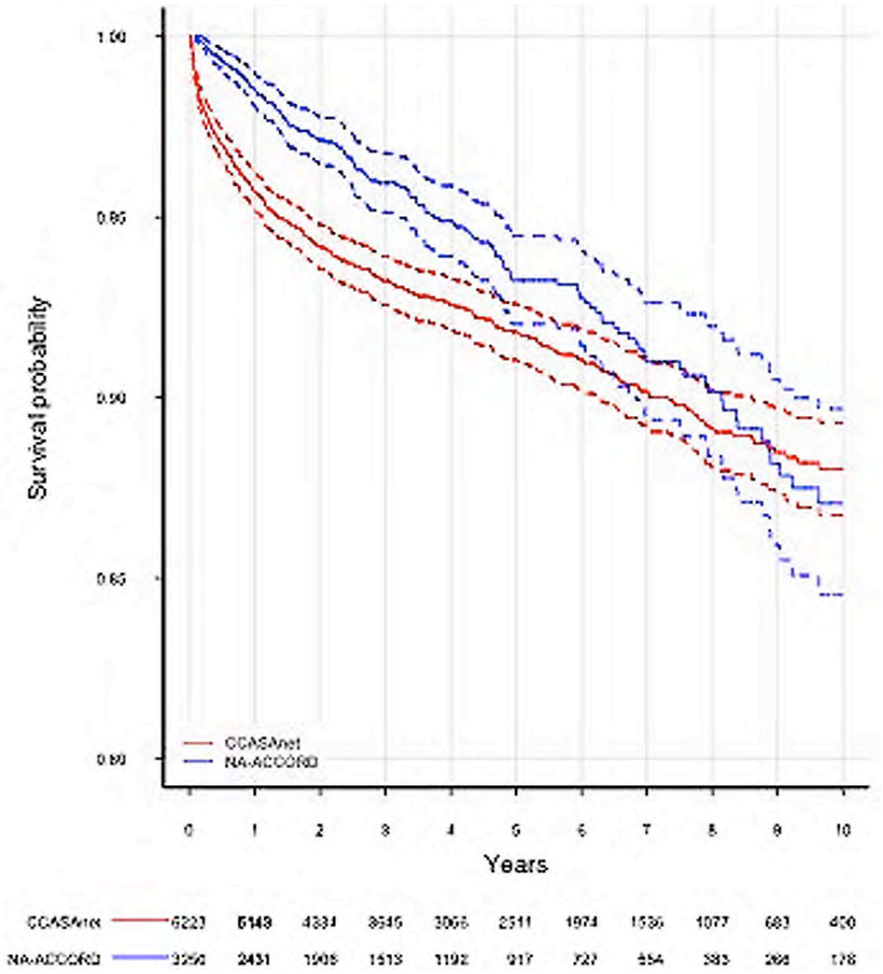


Figure 1: Crude mortality rates among Latino patients at CCASAnet and NA-ACCORD sites

Conclusions: Latinos starting ART in Latin America tended to be more immunosuppressed and to be at higher risk of virologic failure and death than Latinos starting ART in North America. These findings may be due to differences in health care settings, drug combinations prescribed and/or access to care. Further investigation is needed.

581 WITHDRAWN

582 Impact of Specific Antiretroviral Drugs on Non-AIDS Mortality; the D:A:D Study

Camilla I. Hatleberg[1]; Lene Ryom[1]; Andrew N. Phillips[2]; Amanda Mocroft[2]; Peter Reiss[3]; Matthew Law[4]; Rainer Weber[5]; François Dabis[6]; Jens D. Lundgren[1]; Colette Smith[2]
On behalf of the D:A:D Study group

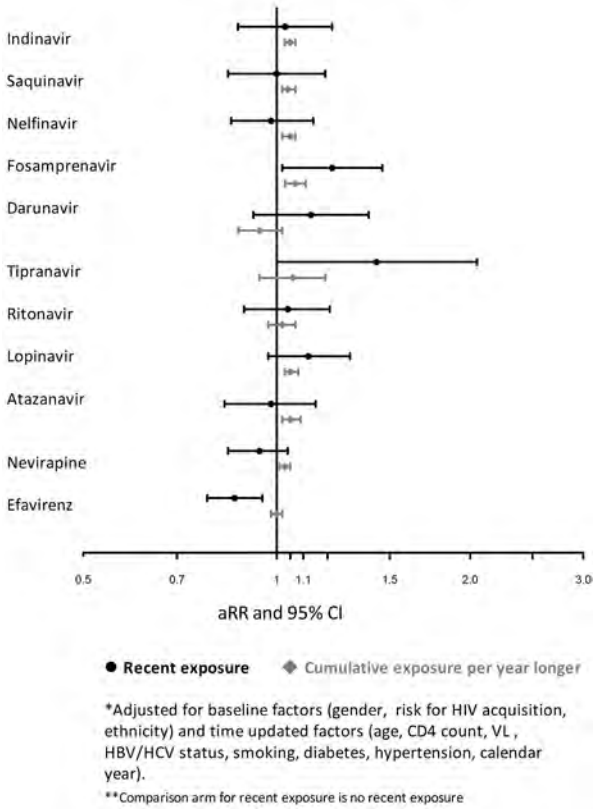
[1]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [2]University College London, London, United Kingdom; [3]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; [4]University of New South Wales, Sydney, Australia; [5]University Hospital Zurich, Zurich, Switzerland; [6]University of Bordeaux, Bordeaux, France

Background: In previous studies, protease inhibitors (PIs) have been associated with an increased risk of death and non-AIDS events, such as cardiovascular events and non-AIDS cancers. We investigated whether specific PIs and non-nucleoside transcriptase inhibitors (NNRTIs) are associated with increased non-AIDS mortality.

Methods: D:A:D study participants were followed from study enrolment until earliest of death, 1/2/2013 or last clinic visit. Exposure to specific PIs/NNRTIs was classified as recent (current use/use in last 6 months) or cumulative (/year). Poisson regression compared relative death rates (RR) for both types of exposure in two separate models. Follow-up among individuals dying from AIDS-related causes was censored on date of death.

Results: 3276 non-AIDS deaths occurred in 371,333 person years (PYRS) (incidence: 8.8/1000 PYRS; 95% CI; 8.5-9.1). In follow-up for which the current CD4 count was >500 cells/mm3, death rates were highest for those currently receiving indinavir (rate: 7.4; 5.4-9.5) and lowest for those currently receiving efavirenz (EFV 4.2; 3.6-4.9). Relative differences were similar across time-updated CD4 /viral load (VL) strata. After adjustment, there was no significant association between recent exposure to commonly used PIs and increased death rates. In contrast, recent exposure to EFV (RR: 0.86) was significantly associated with a decreased death rate (Figure). For cumulative exposure (RR/year longer), the commonly used PIs/NNRTIs lopinavir/ritonavir (LPV/r), atazanavir (ATV), saquinavir (SQV) and nevirapine (NVP) were significantly associated with small increases in death rates (Figure). Corresponding RR/10 years longer were; LPV/r (1.69; 1.36-2.09), ATV (1.69; 1.24; 2.30), SQV (1.50; 1.18- 1.89) and NVP (1.34; 1.14-1.58). Results were consistent across CD4/VL strata; when restricting analyses to those currently on antiretroviral drugs; excluding unknown causes of deaths and excluding intravenous drug users.

Figure: Associations between recent and cumulative exposure to PIs/NNRTIs and non-AIDS mortality*



*Adjusted for baseline factors (gender, risk for HIV acquisition, ethnicity) and time updated factors (age, CD4 count, VL , HBV/HCV status, smoking, diabetes, hypertension, calendar year).
**Comparison arm for recent exposure is no recent exposure

Conclusions: Our findings, based on a substantial sample size, suggest that cumulative exposure to some PI/NNRTIs is associated with a small but gradual increased risk of non-AIDS mortality. This effect is consistent among various types of PIs and of an extent comparable to earlier findings for non-AIDS events. Conversely, recent exposure to EFV was associated with a reduced risk of non-AIDS mortality. Choice of PIs/NNRTIs may affect long-term prognosis and although potential confounding cannot be ruled out, results argue for continued pharmacovigilance.

583 HIV-Related Causes of Death in the Era of Antiretroviral Therapy: Analysis of Verbal Autopsy Data

Clara Calvert[1]; Zehang Li[2]; Tyler McCormick[2]; Alison Price[1]; Kobus Herbst[4]; Denna Michael[3]; Estelle McLean[1]; Basia Zaba[1]; Samuel Clark[2]
On behalf of the ALPHA network

[1]London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]University of Washington, Seattle, WA, US; [3]National Institute for Medical Research, Mwanza, United Republic of Tanzania; [4]Africa Centre for Health and Population Studies, Mtubatuba, South Africa

Background: Mortality rates remain higher in HIV positive than HIV negative individuals despite the introduction of antiretroviral therapy (ART). Understanding the causes of death in HIV positive individuals, and how these have altered with ART treatment, will help direct interventions to prevent these deaths. Since causes of death are not medically certified in sub-Saharan Africa we rely on interpretation of verbal autopsy data to generate cause of death information.

Methods: We used verbal autopsy data collected in three community-based HIV cohorts from Tanzania (Kisesa), Malawi (Karonga) and South Africa (uMkhanyakude), which form part of the ALPHA network. Data on symptoms and circumstances were processed using the InSilicoVA algorithm, and cause of death distributions were classified by ART availability and HIV status of the deceased. The percentage of deaths assigned to HIV/AIDS using the algorithm were compared to age-standardized HIV attributable mortality. HIV attributable mortality (PAF) was calculated by comparing the observed numbers of deaths in HIV positive individuals to the number expected if age-specific mortality rates were the same as those observed in the HIV negative group.

Results: Following ART introduction, there were substantial declines in the percentage of deaths assigned to HIV/AIDS. The most dramatic declines were observed in Kisesa, where the percentage of deaths assigned to HIV/AIDS dropped from 43% in the pre-ART era to 26% once ART became widely available, compared to a decline from 36% to 32% in the PAF. Amongst HIV positive individuals in Kisesa the percentage of deaths assigned to TB increased with ART availability for both males (from 26.3% to 36.3%) and females (from 27.9% to 33.9%); neoplasms increased in females (from 4.3% to 10.1%) but not males where they remained at 8.0%. In uMkhanyakude there was a large increase in the percentage of HIV positive female deaths assigned to TB (from 24.8% to 36.5%) but no such trend was observed in males. There were no substantial changes in the percentage of deaths attributed to non-communicable diseases in uMkhanyakude.

Conclusions: Increases in the percentage of deaths from neoplasms among the HIV positive are to be expected as deaths from classic HIV-related causes are suppressed by ART. The fact that TB continues to rise as a proportion of all assigned causes among the HIV-positive suggests better management of TB cases is needed at treatment start.

584 Facility-Level Factors Associated With Mortality of Patients on ART: A Retrospective Cohort Study in Kenya, 2007-2012

Emily A. Dansereau[1]; Allen Roberts[1]; Herbert C. Duber[1]; Gregoire Lurton[1]; Brendan DeCenso[2]; Thomas Odeny[1]; Samuel Masters[3]; Roy Burstein[1]; Pamela Njuguna[1]; Emmanuela Gakidou[1]
[1]University of Washington, Seattle, WA, US; [2]RTI International, Raleigh, NC, US; [3]University of North Carolina, Chapel Hill, NC, US

Background: While the individual-level benefits of antiretroviral therapy (ART) are well established, much remains to be understood about the population-level impacts of ART scale-up in Kenya and other Sub-Saharan African countries. Most knowledge of mortality levels and determinants comes from relatively small or unrepresentative study sites that may not accurately reflect full national programs. In this study we analyze data from a large sample of Kenyan ART facilities, representing the general population receiving ART.

Methods: We randomly extracted between 50 and 250 adult ART charts at a nationally-representative sample of Kenyan facilities. The charts were paired with a survey of facility resources and practices. A competing risk analysis was used to calculate crude cumulative mortality and loss to follow up (LTFU) after 6, 12 and 24 months on treatment. Adjusted mortality was also calculated for the same time points, which included a correction to account for death among LTFU patients. The correction was estimated at the facility-level, based on a meta-analysis of prior literature demonstrating the relationship between total percent LTFU and the percent of those that had died. Additional analyses examined cumulative mortality stratified by sex, and initial CD4. Regression analysis was done at the facility-level to assess predictors of adjusted mortality rates.

Results: We extracted charts from 16,015 adult ART patients across 63 facilities. The crude cumulative mortality rate was 7%, 9% and 10% at 6, 12 and 24 months respectively. Cumulative LTFU for the same points was 22%, 27%, and 34%. After applying the LTFU correction, adjusted cumulative mortality was 14%, 17% and 18% at 6, 12 and 24 months. Public and rural facilities had significantly higher mortality rates, after controlling for the demographic and clinical composition of their patient populations. Other program characteristics, including nurse-led treatment, were not significant predictors.

Conclusions: The adjusted mortality rates contribute important information about outcomes for a large, unbiased sample of Kenyan patients. Differences in mortality by location and ownership suggest the presence of inequities affecting rural and public clinics. The lack of significant differences across other dimensions indicates that comparable care may be possible with cost-saving changes such as task-shifting.

THURSDAY, FEBRUARY 26, 2015

Session P-L1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HIV Drug Resistance: Mechanisms and Mutations

585 Structural Basis of Inhibition and Resistance Mechanism to EFdA, a Highly Potent NRTI

Zhe Li[1]; Karen Kirby[1]; Bruno Marchand[1]; Michailidis Eleftherios[1]; Eiichi Kodama[2]; Hiroaki Mitsuya[3]; Michael Parniak[4]; Stefan Sarafianos[1]
[1]University of Missouri, Columbia, MO, US; [2]Tohoku University, Sendai, Japan; [3]National Institutes of Health, Division of AIDS, Bethesda, MD, US; [4]University of Pittsburgh, Pittsburgh, PA, US

Background: Unlike any current clinical nucleoside reverse transcriptase inhibitors (NRTIs), 4′-ethynyl-2-fluoro-2′-deoxyadenosine (EFdA) retains a 3′-OH. EFdA has exceptional potency *in vivo* and *in vitro*, highly efficient against drug-resistant strains and has outstanding specificity index. EFdA can act as an immediate or as a delayed chain terminator, by affecting translocation of RT after its incorporation in the nascent DNA chain. It can also be efficiently misincorporated by RT, leading to mismatches that are hard to extend and also protected from excision. The M184V mutation causes mild resistance to EFdA (7.5 fold). To unravel the structural basis of EFdA's extraordinary activity, unique set of inhibition mechanisms and excellent resistance profile, we solved crystal structures of RT (wild-type and M184V) in complex with DNA and EFdA-triphosphate (TP) or with DNA that has EFdA incorporated in it.

Methods: Dideoxy-terminated DNA containing a thioalkyl tethered guanosine was covalently cross-linked to RT, mixed with EFdA-TP and crystallized to obtain RT/DNA_{dd}/EFdA-TP complexes. RT-terminated with EFdA at the primer terminus (RT/DNA_{EFdA}) was also crystallized. Crystals were dehydrated, flash-cooled in liquid N_2, and diffraction data were collected at Advanced Light Source.

Results: The ternary complex structure of wild-type RT/DNA_{dd}/EFdA-TP was solved at 2.4 Å resolution. This structure reveals the atomic interactions of EFdA-TP that make it a tight binder at the pre-translocation site, thus preventing RT translocation and explaining the inhibition mechanism as a translocation-defective RT inhibitor. Comparison of the 2.9 Å RT_{M184V}/DNA_{dd}/EFdA-TP structure with control structures RT_{M184V}/DNA_{dd}/dA-TP or RT_{M184V}/DNA_{dd}/4′-Ethyl-dA-TP (2.9 Å and 3.2 Å) explain how this mutation affects molecular interactions with EFdA and influences its potency, enhancing our understanding of why resistance to EFdA is difficult to develop. A 2.8 Å structure of an RT/DNA complex with an EFdA-MP incorporated at the 3′ primer end and further extended by a mismatched second EFdA-MP (RT/$DNA_{EFdA\text{-}MP}$–$_{EFdA\text{-}MP}$)also provides insights into the structural details of EFdA in the translocation process as well as mismatched incorporation.

Conclusions: The 4′-ethynyl group of EFdA-TP or EFdA-MP-terminated DNA can bind tightly at a polymerase active site hydrophobic pocket, suppressing translocation and inhibiting further DNA synthesis. The M184V mutation mildly decreases EFdA-TP binding through interactions with the 4′E.

586 Structural Basis and Distal Effects of Gag Substrate Coevolution in Drug Resistance to HIV-1 Protease

Kuan-Hung Lin; Celia A. Schiffer
University of Massachusetts Medical School, Worcester, MA, US

Background: HIV-1 protease is a key antiviral drug target due to its essential function of processing viral polyproteins. Among primary protease mutations, I50V is commonly observed in patients failing therapy with PIs APV and DRV. In addition to conferring resistance to PIs, I50V mutation also impairs substrate processing. Mutations in the p1-p6 cleavage site are statistically associated with I50V protease mutation in the viral sequences retrieved from patients. However, the molecular basis of how compensatory mutations restore substrate recognition in drug resistance is not clear. In this study, we report the structural basis for the co-evolution of I50V/A71V protease with the p1-p6 substrate.

Methods: By applying crystallography method and molecular dynamics simulation, we investigate the structural basis of I50V/A71V protease and p1-p6 substrate co-evolution.

Results: The LP1'F substrate has more vdW contacts with I50V/A71V protease compared to those in either $I50V/A71V_{WT}$ or $WT_{LP1'F}$. This is also the case for the PP5'L substrate. In addition, the LP1'F mutation causes a distal change at the substrate P5' proline that is in an alternative position in the WT complex. This change increases the P5' proline's vdW contacts.

The RP4'S substrate forms an additional hydrogen bond with both WT and I50V/A71V protease through the P4' serine side chain. This extra hydrogen bond may compensate for the loss of vdW contacts due to the smaller size of serine in these two complexes

In LP1'F substrate mutation, the peptide bond between Gly51 and Gly52 in the $I50V/A71V_{PP5'L}$ structure is flipped compared to the other structures, and this flipped peptide bond pushes the 50s loop towards the substrate, causing increased vdW contacts.

In the dynamic conformational ensemble of the WT_{WT} structure, the distance between 80-80 loops is around 17.5 Å, and expands to 19–19.5 Å with mutations in either the protease or substrate, the co-evolution brings this distance back to 17.5–18.0 Å, similar to the WT inter-loop distance.

Conclusions: Coevolving mutations in the substrate enhance substrate–protease interactions through a variety of molecular mechanisms. The effects of substrate mutations are not local, but propagate to distal parts of both the substrate and the protease. Drug resistance mutations in the protease or the substrate disturbed the active site dynamics, which was restored in all co-evolved complexes bearing complementary mutations in both the protease and the substrate.

587 Influence of Codon Pair Usage in the Evolvability of HIV-1

Maria Nevot; Cristina Andrés; Mariona Parera; Glòria Martrus; Miguel Ángel Martínez
IrsiCaixa Institute for AIDS Research, Badalona, Spain

Background: The extraordinarily large number of possible encodings in natural genes is to some extent restricted by two encoding biases referred to as codon bias and codon pair bias. An unexplored aspect of the genetic architecture of HIV-1 is how codon choice influences population diversity and evolvability. Here we compared the development of HIV-1 resistance to protease inhibitors (PIs) of WT virus and a synthetic virus (MAX) carrying a codon-pair re-engineered protease sequence with 38 (13%) synonymous mutations.

Methods: The re-coded protease gene segment (MAX) was synthesized *de novo* and recombined to an HXB2 HIV-1 infectious clone. By serial culture passages WT and MAX viruses were subjected to the selective pressure of PIs [atazanavir (ATV) and darunavir (DRV)].

Results: WT and MAX virus replicated indistinguishably in MT-4 cells or PBMCs. An initial sequence analysis of individual clones demonstrated that after one passage in MT-4 cells WT protease quasispecies diversity (p-distance) was significantly higher than that of the virus carrying the MAX protease either at the nucleotide level (0.0016 ± 0.0001 vs 0.0014 ± 0.0000, p=0.0033, unpaired t test) or at the amino acid level (0.0034 ± 0.0001 vs 0.0023 ± 0.0001, $p < 0.00001$). This result indicated that WT and MAX proteases may occupy different sequence spaces. To explore the evolvability of the codon pair re-coded protease, WT and MAX viruses were growth under the selective pressure of ATV and DRV. After the same number of serial passages in MT-4 cells in the presence of PIs, WT and MAX viruses developed phenotypic resistance to PIs (IC50 14.63±5.39 nM and 21.26±8.67 nM, for ATV; and IC50 5.69±1.01μM and 9.35±1.89 for DRV, respectively). Sequence clonal analysis showed the presence, in both viruses, of resistance mutations to ATV and DRV. However, a different resistance variant repertoire appeared in the MAX virus protease. Specifically, the G16E substitution was only observed in the WT protease. In addition, L10F, L33F, K45I, G48L and L89I substitutions were only detected in the re-coded MAX protease population.

Conclusions: The differences in the mutation pattern that emerged after PIs treatment suggested again that WT and MAX virus proteases occupy different sequence spaces although both virus proteases were able to develop PIs resistance. Further studies will required to elucidate whether HIV-1 sequences have evolved to optimize not only the protein coding sequence but also the DNA/RNA sequences.

588 Four Amino Acid Changes in HIV-2 Protease Confer Class-Wide PI Susceptibility

Dana N. Raugi[1]; Robert A. Smith[1]; Matthew Coyne[1]; Julia Olson[1]; Kara Parker[1]; Selly Ba[2]; Papa Salif Sow[2]; Moussa Seydi[2]; Geoffrey S. Gottlieb[1]
University of Washington-Dakar HIV-2 Study Group
[1]*University of Washington School of Medicine, Seattle, WA, US;* [2]*Centre Hospitalier National Universitaire de Fann, Universite Cheikh Anta Diop de Dakar, Dakar, Senegal*

Background: Protease inhibitor (PI)- based regimens are the mainstay of antiretroviral therapy for HIV-2. However, HIV-2 exhibits some degree of intrinsic resistance to the majority of FDA-approved PI, only retaining clinically-useful susceptibility to lopinavir, darunavir, and saquinavir. The mechanisms for this resistance remain largely unknown; although HIV-1 and HIV-2 proteases share only 40-50% sequence identity, structural studies indicate that the ligand-binding sites differ by just four amino acids. In the current study, we examined the contributions of these four residues to intrinsic PI resistance in HIV-2.

Methods: We used site-directed mutagenesis to construct an $HIV\text{-}2_{ROD9}$ molecular clone in which protease codons 32, 47, 76, and 82 were substituted to encode the amino acids found in wild-type HIV-1 (clone PRΔ4: I32V+V47I+M76L+I82V), as well clones containing each single substitution. We used single-cycle assays to quantify the phenotypic sensitivity of the five mutant clones, as well as wild-type (WT) $HIV\text{-}1_{NL4\text{-}3}$ and $HIV\text{-}2_{ROD9}$, to nine FDA-approved PI. EC_{50} values were calculated from dose-response data using sigmoidal regression and tested for statistically significant differences by ANOVA.

Results: Relative to WT HIV-2, HIV-2 clones containing single amino acid substitutions I32V, V47I, M76L, or I82V conferred effects ranging from no change to a 13-fold decrease in EC_{50}, depending on the PI tested. Clone PRΔ4 displayed significant reductions in EC_{50} (3.6 to 60-fold) to all PI except saquinavir. EC_{50} values for PRΔ4 vs. WT were as follows: saquinavir 12 vs. 31 nM, ritonavir 160 vs. 580 nM, lopinavir 21 vs. 105 nM, tipranavir 120 vs. >1000 nM, indinavir 16 vs. 150 nM, nelfinavir 47 vs. 490 nM, darunavir 2.2 vs. 58 nM, amprenavir 23 vs. >1000 nM, and atazanavir 1.1 vs. 66 nM. EC_{50} values for PRΔ4 were lower than, or equivalent to, those for WT HIV-1.

Conclusions: Taken together, our data show that four amino acid changes in HIV-2 protease are sufficient to confer a pattern of PI susceptibility comparable to that of HIV-1. These findings enhance our overall understanding of the genetic basis of PI susceptibility and show that active site residues in protease are the primary determinants of intrinsic PI resistance in HIV-2.

589 Enhanced Neutralization of HIV-1 With Fusion Inhibitor Resistant Mutations

Muntasir Alam[1]; Takeo Kuwata[1]; Kristel P. Ramirez[1]; Yasuhiro Maruta[1]; Kazuki Tanaka[1]; Kazuya Shimura[2]; Shinya Oishi[2]; Nobutaka Fujii[2]; Masao Matsuoka[2]; Shuzo Matsushita[1]
[1]Kumamoto University, Kumamoto, Japan; [2]Kyoto University, Kyoto, Japan

Background: Fusion inhibitors bind to gp41 heptad repeat 1 (HR1), inhibiting the formation of six-helix bundle structure and subsequently blocking the entry of HIV-1 inside host cell. Several fusion inhibitors with improved potency and stability, such as C34, SC34 and SC34EK, have been developed and shown higher genetic barrier for resistance induction than Enfuvirtide or T-20, the only FDA approved fusion inhibitor. Here we investigated the effect of mutations to escape from these novel fusion inhibitors on sensitivities against neutralizing antibodies.

Methods: HIV-1_{JR-FL} Env glycoprotein gp160 bearing T-20 resistant mutants (V38A, Q40H and N43D) and C34, SC34, SC34EK resistant mutations (selected by in vitro) in gp41 were constructed. In gp41 mutations are distributed among several functional domains including heptad repeat 1 and 2, MPER, immunodominant region, transmembrane domain and cytoplasmic domain. Pseudoviruses expressing these Env were used in neutralization assay with monoclonal antibodies (MAbs) against CD4 binding site (b12, VRC01, 49G2, 82D5, 42F9), V3 loop (1C10, KD247, 16G6), CD4-induced site (916B2, 4E9C), gp41 membrane proximal external region (4E10, 2F5, 10E8) and gp41 (2E8S34). IC_{50} value was calculated from neutralization curves and compared with that of wild type virus.

Results: Pseudoviruses expressing resistant mutant envelopes showed reduced level of infectivity when compared to wild type. Our overall neutralization data indicated that fusion inhibitor resistant mutations in gp41 did not reduce neutralization potency of antibodies tested, rather increased the potency of some antibodies. T-20 resistant mutant N43D showed enhanced neutralization by 4E10 (3.5×), 10E8 (12×) and also by anti-V3 antibodies, 1C10 (3.1x) and KD247 (4.3x). SC34EK-resistant virus was significantly sensitive to anti-MPER antibodies (4E10; 22.8x, 2F5; 20.6x, 10E8; 12.4x). MAb 49G2 and 42F9, which fail to neutralize the wild type JR-FL pseudovirus, neutralized C34 and SC34 resistant mutants. Anti-V3 MAbs neutralized C34, SC34 and SC34EK resistant mutants with 3 to 10 fold lower IC_{50} values than that of wild type.

Conclusions: Our data indicate that, fusion inhibitor resistant mutations in gp41 had impact on major epitopes on gp120 and gp41, enhancing sensitivities to antibodies. Therefore, next generation fusion inhibitors and MAbs could be a potential combination for future regimen of combined antiretroviral therapy.

590 Mutations at the Bottom of the Phe43 Cavity Are Responsible for Cross-Resistance to NBD Analogues

Shigeyoshi Harada[1]; Yu Irahara[2]; Samatchaya Boonchawalit[1]; Mai Goryo[1]; Hirokazu Tamamura[2]; Tetsuro Matano[1]; Shuzo Matsushita[3]; Kazuhisa Yoshimura[1]
[1]National Institute of Infectious Diseases, Shinjuku, Japan; [2]Tokyo Medical and Dental University, Chiyoda, Japan; [3]Kumamoto University, Kumamoto, Japan

Background: CD4 mimic small compounds (CD4MCs), NBD-556 and its analogues, inhibit the gp120-CD4 interaction and can also induce conformational changes in the gp120 architecture thereby exposing masked epitopes of neutralizing antibodies on the Env protein. Recently, some groups have reported novel potent NBD analogues. We designed and synthesized five new NBD analogues (YIR compounds). In this study, we characterized CD4MC-resistant viruses induced by in vitro selection to these novel NBD analogues.

Methods: Resistant variants were induced by five CD4MCs (NBD-556, YYA-021, HAR1-71, JRC-II-191 or HAR-431) using the primary KP-5P virus (subtype B, R5) in PM1 cells. We constructed infectious KP-5P clones with CD4MC-resistant mutation following *in vitro* selection. The susceptibility of the infectious clones to the novel CD4MCs (YIR-327, YIR-329, YIR-438, YIR-501, YIR-504, DMJ-I-228 and DMJ-II-121) and other entry inhibitors (Maraviroc, Cenicriviroc, RPR103611 and IC9564) was tested in a TZM-bl assay.

Results: Resistance against five NBD analogues, NBD-556, YYA-021, HAR-171, JRC-II-191 and HAR-431, was associated with V255M, T375I, or M426I substitutions that line the Phe43 cavity of gp120. Two of three mutated residues, V255M and T375I, are located at the bottom of the Phe43 cavity, while M426I is at the edge of the cavity. Clones V255M or T375I were highly resistant against the five NBD analogues. These mutated clones were cross-resistant to all our novel CD4MCs, YIR-327, YIR-329, YIR-438, YIR-501 and YIR-504, and also to DMJ-I-228, DMJ-II-121. On the other hand, the clone with M426I was more resistant than those with V255M and T375I mutations to sCD4 but not as resistant to the CD4MCs tested, because the Phe43 residue of sCD4 is located at a shallow position in the cavity compared to the CD4MCs. However, the mutated clones retained wild type sensitivity to other entry inhibitors (Maraviroc, Cenicriviroc, RPR103611 and IC9564). These results suggest that two mutations at the bottom of Phe43 cavity are critically important not only for binding but also broad resistance to CD4MCs.

Conclusions: The mutations V255M and T375I at the bottom of Phe43 cavity can induce broad and potent cross-resistance to NBD analogues. These data provide additional knowledge for synthesizing novel NBD analogues with a high genetic barrier.

591 SIV_{mac239} Integrase as a Model of HIV Drug Resistance Against Integrase Inhibitors

Said Hassounah[1]; Thibault Mesplede[1]; Maureen Oliveira[1]; Peter K. Quashie[1]; Daniela Moisi[1]; Paul A. Sandstrom[2]; Mark A. Wainberg[1]; Bluma Brenner[1]
[1]McGill University, Montréal, Canada; [2]National HIV and Retrovirology Laboratory, National Microbiology Laboratory, Public Health Agency of Canada, Ottawa, Canada

Background: We previously showed that SIV_{mac239} is susceptible to raltegravir (RAL), elvitegravir (EVG) and dolutegravir (DTG) with IC_{50}s in the nanomolar range, and integrase (IN) mutant viruses displayed similar resistance profiles to HIV. A long-acting form of a new INSTI termed S/GSK-1265744, a DTG analogue, was shown to protect macaques against repeated vaginal and rectal exposures of SHIV. These studies show that nonhuman primates can be utilized to investigate the potential role of IN strand transfer inhibitors (INSTIs) in HIV therapy, pathogenesis and transmission.

Our objectives were to observe whether HIV and SIV share similar resistance pathways under INSTI pressure in selections and cell-free assays and to test the effects of HIV-1 IN resistance mutations on SIV IN activity.

Methods: Tissue culture selections were performed in rhesus macaques peripheral blood mononuclear cells (PBMCs) infected with SIV_{mac239} viruses in the presence of RAL, EVG and DTG. Viral RNA was extracted from cell culture fluids and sequenced for any changes in the integrase coding region. To elucidate the molecular mechanism of resistance, SIVmac239 IN protein was cloned into a bacterial expression vector, pET15b, and resistance mutations were introduced by site-directed mutagenesis. Purified recombinant SIVmac239 WT, G118R, Y143R, Q148R, N155H, or R263K IN enzymes were obtained and strand transfer activities assessed using cell-free based assays.

Results: After 22 weeks of DTG pressure, an R263K mutation was noted in rhesus macaque PBMCs infected with SIV_{mac239}. Our analysis of IN activity showed that resistance mutations in SIV recapitulate the effects observed in HIV-1. In particular, G118R and G140S/Q148R substitutions decreased target DNA affinity (~5.5 and 2-fold) and enzyme efficiency to 20% and 40% of WT levels, respectively. G140S/Q148R negatively impacted strand transfer activity (70% of WT levels).

Conclusions: This study supports the use of nonhuman primate model to study HIV pathogenesis, therapy and transmission. SIV_{mac239} viruses treated with DTG led to the emergence of R263K, which is similar to the unique pattern of DTG resistance in HIV in participants in the SAILING study. This study further confirms that the same mutations associated with drug resistance in HIV exhibit similar profiles in SIV.

592 Within-Run Cross-Contamination in Deep Sequencing Applications on the Illumina MiSeq

Chanson J. Brumme; Winnie Dong; Celia K. Chui; Richard Liang; Art F. Poon; Richard Harrigan

BC Centre for Excellence in HIV/AIDS, Vancouver, Canada

Background: The Illumina MiSeq DNA sequencing system generates several gigabases of short reads per run with a relatively low error rate. We previously described longitudinal contamination on this platform which has since been addressed by a post-run bleach wash. Here we characterize rates and sources of systematic low level, within-run cross-sample contamination, an under-reported issue for this platform.

Methods: In order to assess cross-contamination observed in previous experiments, two libraries of disparate amplicons (HCV NS5B, human HLA-B) were sequenced at high read depth on a single MiSeq run (v2, 2x250bp). HCV RNA was extracted from 24 patient-derived plasma samples using a NucliSens easyMag, and a 327-bp fragment of NS5B was amplified by nested RT-PCR. Human genomic DNA was extracted from 33 whole blood samples and a region spanning HLA-B exons 2 and 3 was amplified. All stages of HCV and HLA library preparation were performed on different days by different staff. Indexed PCR primers for these targets were ordered months apart, effectively ruling out primer synthesis as a source of cross-contamination. Including replicates, 69 amplicons were sequenced using a total of 56 Illumina index pairs. Sequenced HCV and HLA samples shared either zero, one or two indices with samples of the opposite type. Short read data were cleaned and iteratively mapped using a custom pipeline built around *bowtie2* and *samtools*.

Results: The run cluster density was 940 K/mm^2 with 89% of reads passing filters, suggesting normal instrument performance and library preparation. On average, approximately 141,000, and 177,000-fold coverage was obtained for HCV and HLA-B, respectively. Interestingly, up to 3637 HLA-B reads (1.8% of total reads) were observed in samples expected to contain only HCV, and up to 217 HCV reads (0.09%) were observed in HLA-B samples. Screening all suspected contaminants (e.g. HCV reads in an HLA sample) against all consensus sequences indicated that the source of contamination was far more likely to be a sample that shared one Illumina index than a sample that shared none (OR=15.7, p=10^{-11}). Cross-contamination between reads sharing one index was also observed between samples of the same type.

Conclusions: The MiSeq is subject to low-level cross-contamination from samples that share one "barcode" in a dual-indexing strategy. Accurate interpretation of low-frequency variants detected by deep sequencing requires knowledge of all other samples run on the instrument and their associated barcodes.

593 Analysis of Resistance Haplotypes Using Primer IDs and Next Gen Sequencing of HIV RNA

Valerie F. Boltz[1]; Jason Rausch[1]; Wei Shao[2]; Charles Coomer[1]; John W. Mellors[3]; Mary Kearney[1]; John M. Coffin[4]

[1]National Institutes of Health (NIH), Frederick, MD, US; [2]Leidos, Frederick, MD, US; [3]University of Pittsburgh, Pittsburgh, PA, US; [4]Tufts University, Boston, MA, US

Background: Targeted sequencing technologies using primer IDs can result in more accurate representations of HIV-1 populations but PCR bias and recombination have hampered progress. Here we describe a new method for library construction that produces a larger number of tagged consensus sequences, increases sensitivity of haplotype determination, and reveals the sources of recombination.

Methods: Each molecule of cDNA from mixtures of varying percentages of wild-type and mutant HIV-1 *pol* transcripts containing 14 drug resistance mutations was tagged uniquely using a gene-specific primer with primer IDs. cDNAs were then PCR amplified using two methods: (1) 90mer primers containing required MiSeq sequences; (2) 22mer primers containing uracil followed by digestion, cleavage and ligation to linkers containing MiSeq sequences. DNA was sequenced using paired-end MiSeq Illumina technology and consensus sequences were derived from a super-majority (≥80% consensus) for each unique ID. Consensus sequences were analyzed for PCR bias, errors, recombination, and sensitivity for detecting haplotypes.

Results: Of the total cDNA molecules used as template, amplified cDNA with unique tags ranged from 3-19% for method 1 and from 15-52% for method 2. The average error rates for method 1 and 2 were 9.3x10^{-5} and 1.4x10^{-4}, respectively, both comparable to RT error rates. The PCR recombination rate for method 1 was 0.16% but only 0.01% for method 2. Method 1 was able to detect drug resistance mutations down to 0.01% and method 2 down to 0.001%. The sensitivity of haplotype detection was better for method 2: for samples containing 10% or 1% mutant, method 1 never detected linkage of all 14 mutations, whereas method 2 detected all 14 33-35% of the time. Method 2 always detected linkage of the 8 mutations nearest the 3′ end of the amplicon suggesting that PCR recombination is due to incomplete cDNA synthesis.

Conclusions: A linker ligation method of amplifying tagged cDNA reduced both PCR bias and recombination rate compared to standard methods, and was superior at detecting haplotypes within 200bp of the 3′ end of the template. However, it correctly detected linkage across the entire 570bp amplicon in only 1/3 of sequences, suggesting that cDNA synthesis is typically incomplete leading to PCR recombination and thus limiting sensitivity for detection of linked mutations. Improved methods are needed for cDNA synthesis to increase the reliability of haplotype determination for HIV-1 populations.

THURSDAY, FEBRUARY 26, 2015

Session P-L2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HIV Subtypes and Resistance

594 HIV-1 Subtype Influences the Pathways of Genotypic Resistance to Integrase Inhibitors

Tomas J. Doyle[1]; David Dunn[4]; Rolf Kaiser[3]; Erasmus Smit[10]; Anne-Genevieve Marcelin[5]; Carmen de Mendoza[6]; Javier Martínez-Picado[9]; Federico Garcia[7]; Francesca Ceccherini-Silberstein[8]; Anna Maria Geretti[2] CORONET study group

[1]King's College London, London, United Kingdom; [2]University of Liverpool, Liverpool, United Kingdom; [3]University of Cologne, Cologne, Germany; [4]University College London, London, United Kingdom; [5]Hôpital Pitié Salpetriere, APHM, Paris, France; [6]Hospital Carlos III, Madrid, Spain; [7]University Hospital San Cecilio, Granada, Spain; [8]University of Rome Tor Vergata, Rome, Italy; [9]Institut de Recerca de la Sida, Barcelona, Spain; [10]Birmingham Heartlands Hospital, Birmingham, United Kingdom

Background: The mutational profiles selected *in vivo* by integrase inhibitors (INIs) have been primarily defined within clinical trials that involved predominantly subjects with HIV-1 subtype B infection. CORONET is multicentre surveillance programme that aims to characterise INI-resistance in diverse INI-naïve and INI-experienced European cohorts. This analysis addressed the influence of HIV-1 subtype on pathways of genotypic resistance and cross-resistance observed in raltegravir-experienced patients.

Methods: Integrase sequences produced by Sanger sequencing at 9 clinical centres were analysed centrally to identify major INI resistance-associated mutations (RAMs) as defined by the Stanford interpretation algorithm. Codon usage at major integrase resistance codons was analysed using integrase sequences from INI-naïve patients. Proportions were compared by Fisher's Exact test (2-sided).

Results: Sequences were examined from 255 raltegravir-experienced (subtype B 209/255, 82%) and 533 raltegravir-naïve patients (subtype B 399/533, 75%). Non-B subtypes comprised 11 different variants: the most prevalent were subtype C and CRF02; other variants included A, D, F, G, CRF01, CRF06 and CRF09. Overall 113 (44%) raltegravir-

experienced patients had evidence of ≥1 major INI RAM, predominantly N155H (57, 22%), G140S (33, 13%), Q148H (28, 11%), and Q148R (15, 6%). 36/44 (82%) of patients with mutations Q148H/R/K had co-existing G140A/C/S. G140A/C/S and Q148H/R/K were detected in 36/209 (17%) and 42/209 (21%) subtype B infections, and 1/46 (2%, subtype G) and 2/46 (4% subtype C and G) non-B subtype infections respectively (p=0.005 and p=0.009). As a result, prevalence of predicted cross-resistance to dolutegravir was 42 (20%) vs. 2 (4%) in B vs. non-B subtypes respectively (p=0.009). In INI-naive subtype B sequences, emergence of G140S required a single nucleotide substitution (from GGC or GGT to AGC/AGT). With all the non-B viruses sequences analysed, two substitutions were required to mutate the observed codons (GGA or GGG) to a serine codon.

Conclusions: Sequence differences between HIV-1 subtypes influence the pathways of genotypic resistance to raltegravir and resulting cross-resistance to dolutegravir. Subtype B shows a higher propensity to develop the G140/Q148 pathway compared with predominant non-B subtypes circulating in Europe, which is explained by a different codon usage at the G140 position. These findings carry implications for dolutegravir use in raltegravir- and elvitegravir-experienced subjects.

595 Differences in Resistance Mutations in Non-B Subtypes at First-Line Failure in Africa

Cissy M. Kityo[1]; Sarah Walker[2]; Immaculate Nankya[1]; Anne Hoppe[2]; Jennifer Thompson[2]; Silvia Bertagnolio[3]; Philippa Easterbrook[3]; Peter Mugyenyi[1]; Nicholas Paton[4]
On behalf of the EARNEST Trial Team

[1]Joint Clinical Research Centre, Kampala, Uganda; [2]MRC Clinical Trials Unit at University College London, London, United Kingdom; [3]World Health Organization, Geneva, Switzerland; [4]Yong Loo Lin School of Medicine, Singapore, Singapore

Background: Resistance mutations may vary by viral subtype, although data to date are limited, especially for non-B subtypes. Understanding the common mutational patterns is important for determining the optimal standardised regimens for the public health approach to ART in settings without resistance testing or individualised therapy.

Methods: Genotypes were obtained from stored baseline samples from 792 patients aged ≥12 years who met WHO treatment failure criteria after >12 months on NNRTI-based first-line ART in the EARNEST trial in 4 sub-Saharan African countries. Subtype and drug susceptibility were determined by REGA and Stanford algorithms respectively. Presence of specific mutations and intermediate-high level resistance was modelled using multivariable logistic regression including subtype, ART exposure at time of first-line failure, ART prior to the failing regimen, years on first-line ART, and WHO 4 events, CD4 and VL at failure.

Results: Patients had advanced treatment failure (42% VL≥100,000 c/ml, 63% CD4<100 cells/mm^3). Viral subtypes were A1 (40%; Uganda, Kenya), C (31%; Zimbabwe, Malawi) and D (25%; Uganda, Kenya) with 4% recombinants/unclassified. One or more major NRTI or NNRTI mutations were found in 774 (98%) and mutations to both classes in 747 (94%). In adjusted analyses, 4 NRTI and 7 NNRTI mutations differed significantly across the three subtypes (p<0.05; Table 1); most of these 11 mutations were significantly more common in subtype C than in A and/or D. Intermediate/high level TDF resistance (seen in 57%) was independent of subtype (adjusted p=0.38). Intermediate/high level ZDV resistance (in 71% overall) was marginally more common in subtype C (78% (adjusted) than D (76%, p=0.05) and A (76%, p=0.06). Intermediate/high level resistance to ETR or RPV (in 51% and 62% respectively overall) was more common in subtype C (adjusted 63% and 76% respectively) than D (51% and 59% respectively, p<0.02) and A (47% and 60% respectively, p<001). Just 46% patients would be switched to a second-line regimen with predicted ≥1 active NRTI using the WHO algorithm (based on first-line NRTI history), but genotyping would identify a more active regimen in only an additional 35 (4%).

Mutation	Subtype A	Subtype C	Subtype D	Overall P	Pattern
Q151M	1%	11%	0%	<0.001, *¶	C > (A & D)
K65R	9%	13%	6%	0.002, *¶	C > (A & D)
TAM 2	61%	57%	53%	0.01, ¶†	(A & C) > D
L210W	33%	19%	33%	0.04, *¶	(A &D) > C
V106M	0%	16%	1%	<0.001, *¶	C > (A & D)
E138A	5%	10%	3%	0.004, *¶	C > (A & D)
H221Y	22%	28%	12%	0.003, ¶†	(C & A) > D
K101E	11%	22%	19%	0.02, *†	(C & D) > A
Y181C	31%	47%	33%	0.03, *	C > A
V108I	14%	17%	25%	0.01, †	D > A
P225H	8%	1%	11%	0.01, *¶	(A & D) > C

*P < 0.05 for C vs A; ¶P < 0.05 for C vs D; †P < 0.05 for D vs A

"Prevalence of resistance mutations by subtype"

Conclusions: We found differences between subtypes in resistance mutations at first-line failure. The impact on residual NRTI drug susceptibility was modest. However, subtype C developed higher rates of ETR and RPV resistance, limiting their potential utility in salvage regimens in resource-limited settings.

596 K65R Detected More Frequently in HIV-1 Subtype C Viruses at Virological Failure

Erasmus Smit[1]; **Ellen White**[7]; Duncan Clark[4]; Duncan Churchill[2]; Hongyi Zhang[6]; Simon Collins[5]; Deenan Pillay[3]; Anna Tostevin[7]; David Dunn[7]
UKHDRD and UKCHIC

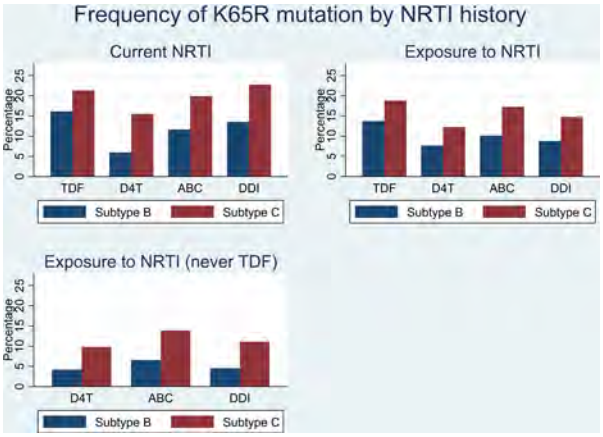
[1]Public Health England, Birmingham, United Kingdom; [2]Brighton and Sussex Hospitals NHS Trust, Brighton, United Kingdom; [3]University of KwaZulu-Nata and University College London, London, United Kingdom; [4]St Batholomew's and the London NHS Trust, London, United Kingdom; [5]HIV i-Base, London, United Kingdom; [6]Addenbrooke's Hospital, Cambridge, United Kingdom; [7]University College London, London, United Kingdom

Background: Theoretically, HIV-1 subtype C viruses have a greater propensity to develop a K65R mutation due to silent nucleotide polymorphisms at nearby codons (64-66) and/or TAM codons which affect the probability of G⟶A transition. Although a high prevalence of K65R has been documented in Southern Africa cohorts, it is unclear whether this is explained by subtype per se or more general characteristics of these cohorts e.g. prolonged time on a failing regimen. We have exploited the diversity of viral subtypes within the UK to undertake a direct comparative analysis of this issue.

Methods: We analysed patients infected with HIV-1 subtype B or C virus who had a resistance test (1996-2013) following virological failure (VF), regardless of type or line of regimen. Sequences with no major IAS-defined mutations were excluded; for patients with ≥2 tests, we selected the first test if K65R was ever detected or the last test if never detected. Prevalence of K65R was related to subtype and exposure to the NRTIs that primarily select for this mutation (TDF, ABC, ddI, d4T). Exposure was considered both as "current" (regimen at time of VF) and any previous exposure. A multivariate logistic regression model quantified the effect of subtype on the prevalence of K65R, adjusting for previous and current exposure to all four specified drugs.

Results: 4,242 patients (3,439 subtype B, 803 subtype C) met the inclusion criteria. Subtype B patients were mostly MSM (77%), and those with subtype C mostly heterosexual (82%, F:M ratio=1.8). Overall, K65R was detected in 7.8% subtype B patients (median 5.0 years [IQR 1.6-7.8] after initiating ART) compared with 14.5% subtype C patients (2.5

years [0.8-5.1]). The subtype difference in K65R prevalence was observed irrespective of NRTI exposure, and K65R was frequently selected by ABC, ddI, and d4T in patients with no previous exposure to TDF (Figure). Multivariate logistic regression confirmed that K65R was significantly more common in subtype C viruses (odds ratio 1.95, 95% CI: 1.51-2.51, P<0.001).



Conclusions: These clinical data complement experimental evidence that K65R is more likely to be detected at VF for subtype C viruses compared with subtype B viruses.

597 Viral Failure and High K65R in Kenyan Patients on Tenofovir-Based First-Line Therapy

Katherine C. Brooks[2]; Lameck Diero[1]; Allison Delong[2]; Maya Balamane[2]; Marissa Reitsma[2]; Emmanuel Kemboi[3]; Millicent Orido[3]; Mia Coetzer[2]; Joseph Hogan[2]; Rami Kantor[2]

[1]Moi University, Eldoret, Kenya; [2]Brown University, Providence, RI, US; [3]Academic Model Providing Access to Healthcare, Eldoret, Kenya

Background: Tenofovir (TDF)-based 1st-line antiretroviral therapy (ART) is globally recommended by the World Health Organization (WHO). Effects of switching from prior non-TDF to TDF-based regimens on ART success are unknown. High rates of the TDF-associated K65R mutation in HIV-1 subtype C, but not B, are reported, associated with a poly-A template in reverse transcriptase (RT) positions 64-66. Such mechanisms in other HIV-1 subtypes are not well-defined.

Methods: We examined treatment failure and resistance in Kenyan patients on ≥6 months of TDF-based 1st-line ART at the academic model providing access to healthcare (AMPATH). We compared these outcomes among patients with (Prior-ART Group) and without (TDF-Only Group) prior non-TDF-based 1st-line ART. *Pol* sequences of patients with detectable VL (>40 copies/mL) were interpreted with Stanford Database tools using Fisher exact and Wilcoxon tests.

Results: Among 332 enrolled patients (55% female, median age 41 years, 63% XTC/TDF/nevirapine; 37% XTC/TDF/efavirenz; median CD4 336 cells/μL), detectable VL was in 17%, and VL>1,000 copies/mL (WHO cutoff) in 10%. Of those, 216 were in the TDF-Only Group (median 20 months on ART), and 116 in the Prior-ART Group (median 24 months on TDF-based ART and 47 months on prior ART). Detectable VL was in 23% of the TDF-Only Group and 7% of the Prior-ART Group (p<.001*)*. TDF-only failing patients had lower CD4 values (p<.001) and higher WHO stage (p=.03). VL>1,000 copies/mL was seen in 15% of the TDF-Only Group and 1% of the Prior-ART Group (p<.001). In 35 available genotypes from the TDF-Only Group 69% were subtype A, 11% D, 12% C and 9% AD. RT resistance was in 89%, 89% to NNRTIs, 83% to NRTIs and 83% dual-class. K65R occurred in 69% (24/35) of patients*;* subtype C 100% (4/4), subtype A 71% (17/24) and subtype D 50% (2/4) (p=.22). Patients with K65R had lower CD4 values (p<.02), higher WHO stage (p=.004) and more RT resistance mutations (p<0.001). Examination of RT positions 64-66 from subtype A infected ART-naïve persons from the same Kenya clinic (n=32) and from the Stanford Database (n=3,903), demonstrated similarity to subtype B, without the poly-A chain that promotes K65R in subtype C.

Conclusions: In this Kenyan cohort, switching from non-TDF to TDF-based 1st line ART was successful. Higher failure rates were seen in patients with only TDF-based ART compared to those with prior 1st-line ART exposure. High observed K65R rates in subtype A were not explained by the poly-A template, suggesting alternative mechanisms.

THURSDAY, FEBRUARY 26, 2015

Session P-L3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Transmitted HIV Drug Resistance: Assessing the Threat

598 Large NNRTI-Resistant Transmission Cluster in Injection Drug Users From Saskatchewan

Alexander Wong[1]; Jaspreet Kambo[1]; Richard Harrigan[2]; Art F. Poon[2]; Jeffrey B. Joy[2]

[1]University of Saskatchewan, Regina, Canada; [2]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada

Background: Saskatchewan, a Canadian Prairie province, is currently experiencing a unique HIV epidemic characterized by high rates of transmission through injection drug use. Aboriginal peoples are disproportionately affected.

Methods: We reviewed the epidemiologic and clinical characteristics of all HIV-positive individuals who attend the Regina Qu'Appelle Health Region Infectious Diseases Clinic, which serves the southern half of Saskatchewan and represents 25% of the province's HIV burden. Molecular phylogenies were inferred from anonymized bulk HIV-1 *pol* sequences from pre-therapy resistance genotyping of all patients for whom testing was available. Short tip-to-tip distances (patristic distance < 0.02) between sequences from different individuals on the phylogeny were used to define clusters. Resistance data was super-imposed on phylogenetic trees to identify clusters of primary transmitted drug resistance.

Results: 415 individuals were included in the analysis. 227/415 (54.6%) were Aboriginal, 246/415 (59.2%) had injection drug use as their primary risk factor for HIV acquisition, and 243/415 (58.5%) were positive for hepatitis C antibody. Through phylogenetic analysis, a large transmission cluster of 81 individuals (19.5% of clinic) was identified in which 76 individuals were harbouring a G190A mutation in the reverse transcriptase gene, conferring NNRTI resistance. Compared to the overall clinic population, individuals with a G190A mutation in this cluster were more likely to be Aboriginal (58/76 [76.3%], RR 1.5, $P < 0.01$), have injection drug use as their primary risk for acquisition of HIV (63/76 [82.9%], RR 1.5, $P < 0.01$), and be co-infected with hepatitis C (64/76 [84.2%], RR 1.6, $P < 0.01$). 10 other clusters were identified but were of smaller size (≤ 18), and none were associated with transmitted drug resistance.

Conclusions: We describe a cluster of 76 individuals with primary transmitted NNRTI resistance to HIV in southern Saskatchewan, characterized by disproportionate transmission through injection drug use in Aboriginal peoples and high rates of hepatitis C co-infection. This represents a microcosm of the current provincial HIV epidemic. Similar transmission clusters are occurring elsewhere across the province, both in urban and on-reserve settings, where prevalence of injection drug use is high. These transmission dynamics, complicated further by social, cultural and geographic factors, require urgent attention and mobilization of public health and clinical resources.

599 Transmitted Drug Resistance and Time of HIV Infection, New York State, 2006-2013

Zhengyan Wang[1]; Emily Walits[2]; Daniel E. Gordon[1]; Bridget J. Anderson[1]; Deepa Rajulu[1]; Ling Wang[1]; Lou C. Smith[1]
[1]New York State Department of Health, Albany, NY, US; [2]University at Albany, School of Public Health, Albany, NY, US

Background: The date of HIV infection cannot be readily established for most HIV cases. Resistance results for persons newly diagnosed with HIV infection may reflect transmissions that occurred years earlier. This study evaluates the need to classify newly diagnosed cases by recency of infection in order to accurately determine the prevalence of transmitted drug resistance (TDR) and assess variation in TDR prevalence across demographic and risk groups in New York State (NYS).

Methods: Newly diagnosed cases 1/2006-9/2013 age ≥13 years in the NYS HIV surveillance registry were classified as "recent" or "longstanding" infections based on BED test results. Absent a BED result, cases with an AIDS diagnosis at or within 6 months of HIV diagnosis were classified as longstanding; all others were classified as "unknown." All cases were linked with clinical genotypic resistance test results routinely reported to NYS Department of Health (NYSDOH). Tests within 3 months of the HIV diagnosis date were considered "initial" resistance tests and were included in the analyses. Mutations in protease (PR) and reverse transcriptase (RT) gene sequences were compared to CDC's Transmitted Drug Resistance Mutation (TDRM) list to assess the presence of TDRMs. Prevalence ratios (PR) of TDRM between recent and longstanding cases were examined.

Results: Among 29,000 newly diagnosed cases, 13,015 (44%) had a resistance test within 3 months of diagnosis. 2,016 (15%) were classified as recent, 8,703 (67%) as longstanding and 2,296 (18%) as missing. Demographic and resistance results for the "missing" group were similar to those for the combined recent and longstanding groups. The rate of TDR among recently infected cases rose from 17% in 2006 to 24% in 2013, from 13% to 18% in cases with longstanding infection and from 13% to 19% in all cases regardless of recency. Prevalence of TDRM was significantly higher among recently infected (19% versus 15%; PR: 1.29, 95% CI: 1.16-1.43) across all subgroups - sex, age, race/ethnicity, risk, and geographic location.

Conclusions: Recency of infection is an important covariate of TDR prevalence among persons newly-diagnosed with HIV. Increasing TDR prevalence among recently infected cases suggests a growing number of transmissions are due to non-ARV naïve persons with poorly controlled infections. Lower TDR prevalence seen in longstanding cases in all years supports this, though overgrowth of resistant strains by wild-type virus over time would also contribute to that group's lower TDR rate.

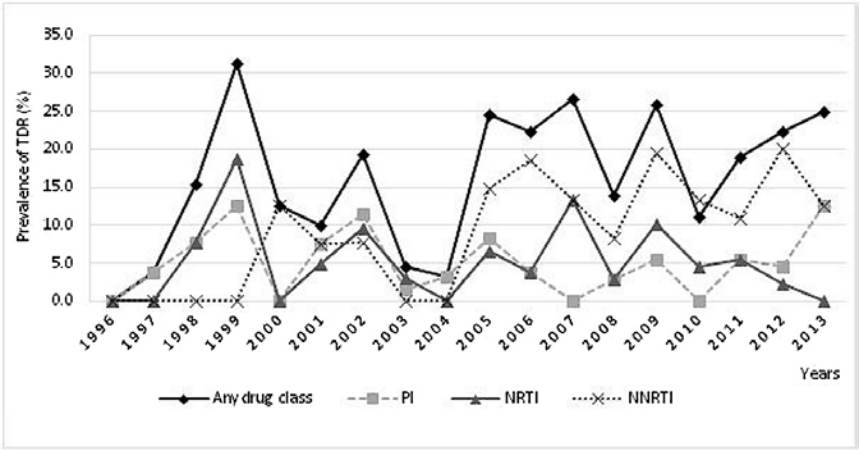
600 Transmitted HIV Drug Resistance Among Early Infected Persons in San Diego, California

Theppharit Panichsillapakit[1]; David M. Smith[2]; Joel Wertheim[2]; Douglas D. Richman[2]; Susan Little[2]; Sanjay Mehta[2]
[1]Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [2]University of California San Diego (UCSD), La Jolla, CA, US

Background: Transmitted HIV drug resistance (TDR) continues to be an important issue, particularly for the initiation of antiretroviral therapy (ART). This study determined the prevalence and phylogenetic relationships of TDR among ART-naïve, HIV-infected individuals in San Diego County from 1996-2013.

Methods: Retrospective analysis of the University of California, San Diego Primary Infection Resource Consortium from 1996 through 2013 was performed. Data were analyzed from 690 participants who underwent genotypic resistance testing before initiating therapy. Mutations associated with TDR were identified according to the WHO-2009 surveillance list. Clustering analysis of the HIV-1 *pol* sequence was performed using a network approach in which putative linkages were inferred when the TN93 genetic distance between two sequences was less than 1.5% substitutions per site.

Results: The overall prevalence of TDR was 16.2% [112/690; 95% confidence interval (CI): 13.6-19.2] with a significant increase throughout the study period (p for trend = 0.009). TDR was predominantly observed for resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) [10.1% (70/690); 95% CI: 8-12.7] and significantly increased over time (p for trend < 0.001). TDR to nucleotide reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) was 5.5% (38/690; 95% CI: 4-7.6) and 4.9% (34/690; 95% CI: 3.5-6.9) respectively, and changed minimally over time. Two and three-class TDR was prevalent at 4.8% and 0.9%, respectively. Among all the individuals with TDR, a total of 219 major and 6 minor TDR mutations were detected. TDR prevalence did not differ according to age, gender, race/ethnicity or risk exposure. 103 transmission clusters were identified of which 11 included at least two individuals sharing the same resistance mutation, accounting for 23.7% of the individuals with TDR.



Conclusions: Between 1996 and 2013, the prevalence of TDR to ART (NNRTIs in particular) significantly increased among ART-naïve individuals with recent HIV-1 infection in San Diego. We found evidence of spread of these drug resistance mutations within transmission clusters of recently infected individuals. These findings continue to highlight the importance of baseline resistance testing to guide healthcare providers to select appropriate therapeutic options and to continue surveillance for drug resistance.

601 HIV Molecular Epidemiology and Transmitted Drug Resistance in the Mesoamerican Region

Claudia Garcia-Morales[1]; Santiago Avila-Rios[1]; Daniela Tapia-Trejo[1]; Carlos Mejía-Villatoro[2]; Juan M Pascale[3]; Guillermo Porras-Cortes[5]; Ivette Lorenzana[4]; Elsa Palou[4]; Marvin Manzanero[6]; Gustavo Reyes-Terán[1]

[1]National Institute of Respiratory DIsease, Mexico City, Mexico; [2]Roosevelt Hospital, Guatemala City, Guatemala; [3]Gorgas Memorial Institute for Health Studies, Panama City, Panama; [4]Universidad Nacional Autónoma de Honduras, Tegucigalpa, Honduras; [5]Vivian Pellas Metropolitan Hospital, Managua, Nicaragua; [6]Ministry of Health, Belize City, Belize

Background: Transmitted drug resistance (TDR) remains an important concern for the management of HIV infection, especially in countries that have recently scaled-up antiretroviral treatment (ART) access. We present preliminary results from a large study to assess HIV TDR and viral diversity in Mexico and Central America.

Methods: HIV-infected ART-naïve individuals from Mexico (n=1476), Guatemala (n=1180), Panama (n=238), Nicaragua (n=222), Honduras (n=294) and Belize (n=100) were enrolled from October 2010 to July 2014. Plasma HIV *pol* sequences were obtained. HIV subtyping was performed with REGA Subtyping Tool v2 and RIP 3.0, available on line. TDR was assessed using the WHO TDR surveillance mutation list.

Results: Belize showed the highest global TDR prevalence (19.0%), followed by Nicaragua (14.9%), Panama (12.2%), Honduras (9.9%, p=0.02), Mexico (7.7%, p=0.0005) and Guatemala (7.1%, p=0.0002). TDR to NNRTIs was higher compared with NRTIs and PIs in Guatemala (4.6%, 1.8% [p<0.0002] and 1.1% [p<0.0001] respectively), Panama (9.2%, 3.8% [p=0.02] and 0.8% [p p<0.0001]), Honduras (6.5%, 2.0% [p=0.01] and 2.2% [p=0.01]) and Belize (18.0%, 1.0% [p<0.0001] and 1.0%[p<0.0001]). Belize showed higher TDR to NNRTIs than Panama (p=0.02), Nicaragua (p=0.002), Honduras (p=0.001), Guatemala (p<0.0001) and Mexico (p<0.0001). Nicaragua showed higher TDR to NRTIs than Panama (p=0.04), Belize (p=0.01), Honduras (p=0.0008), Mexico (p=0.0005), and Guatemala (p<0.0001). In all countries, clusters of drug-resistant viruses were observed. The TDR mutations identified in clusters were M46IL and L90M to PIs, M41L and T215X to NRTIs and K103NS and G190A to NNRTIs. Considering individuals in early chronic stage (>500 CD4+ T cells/uL) vs. late chronic stage (<350 CD4+ T cells/uL) global TDR in Mexico was 9.7% vs 6.5% (p=0.02), and in Guatemala 9.3% vs 6.6% (p=0.0305). HIV subtype B was highly prevalent in Mexico (97.1%), Guatemala (94.5%), Panama (95.0%), Nicaragua (95.9%), Honduras (94.9%) and Belize (67.4%). Country-specific viral clusters were highly frequent, suggesting an important role of cultural and geographic barriers for HIV dispersion in the region.

Conclusions: The global TDR prevalence in Mexico, Guatemala, Panama, Nicaragua and Honduras remains at the intermediate level, but is high in Belize. Different epidemiologic scenarios can be observed in different Mesoamerican countries warranting local HIV molecular epidemiology and TDR surveillance studies.

602 Temporal Trends of Transmitted HIV Drug Resistance Following Seroconversion

Ashley Olson[1]; Claudia Kucherer[3]; Anders Sönnerborg[4]; Carmen de Mendoza[5]; Robert Zangerle[6]; Maria Prins[9]; John Gill[2]; Anne-Marte Bakken Kran[7]; Dimitrios Paraskevis[8]; Kholoud Porter[1]
for CASCADE collaboration in EuroCoord

[1]University College London, London, United Kingdom; [2]University of Calgary, Alberta Health Services, Calgary, Canada; [3]Robert Koch Institute, Berlin, Germany; [4]Karolinska Institutet, Stockholm, Sweden; [5]Puerta de Hierro Research Institute and University Hospital, Madrid, Spain; [6]Innsbruck Medical University, Innsbruck, Austria; [7]Oslo University Hospital, Oslo, Norway; [8]University of Athens, Athens, Greece; [9]Public Health Service of Amsterdam, Amsterdam, Netherlands

Background: Transmitted drug resistance (TDR) may increase with wider use of cART and can contribute to cART failure. We aim to analyse the time trends of TDR among HIV seroconverters.

Methods: Using CASCADE data, we considered nucleotide sequences from ART naïve individuals collected in the cART era (>1996) from samples taken within one year of HIV seroconversion (SC) and identified the most commonly observed (>10%) transmitted mutations by drug class according to the WHO criteria (SDRMs). The virus was considered resistant if a SDRM mutation was present. Using logistic regression, we examined the association between TDR and calendar time (modelled linearly), sex, transmission risk group, acute HIV infection (laboratory evidence of SC or HIV test interval < 30 days) and SC age. To allow 1 year of sample collection after HIV SC, we considered individuals seroconverting until 31 December 2012.

Results: Of 4183 eligible individuals seroconverting 1996-2012 (median 2007), 3839 (92%) were male. Median (IQR) age at SC was 33 (27, 39) and mode of infection was mainly sex between men, 3341 (80%). HIV Subtype was predominantly B, 3041 (73%), followed by A, 315 (8%), C, 263 (6%), and CRF02_AG, 84 (2%). Time from SC to sample collection was similar in those with and without TDR, median = 94 (33, 185) days. Overall, 457 (11%) individuals had ≥1 WHO defined mutation; 251 individuals with NRTI mutations, most commonly at 41L (31%), 215S (21%), 215D (15%) and 184V (12%); 157 individuals with NNRTI mutations, most commonly at 103N (66%); and 125 individuals with PI mutations, most commonly at 90M (26%), 46I (22%), 46L (17%), 82A (13%) and 85V (10%). There was evidence of decreasing TDR to any class from 1996-2012 (OR (95% CI) = 0.918 (0.895, 0.942), p < 0.001) per year increase). The same decreasing trend was seen with NRTIs (OR = 0.881 (0.853, 0.911), p<0.001), NNRTIs (OR = 0.965 (0.925, 1.008), p = 0.11) and PIs (OR = 0.915 (0.874, 0.958), p <0.001). There was moderate evidence of an increased risk of TDR with acute infection (OR = 1.18 (0.96, 1.46), p=0.12).

Conclusions: Transmitted drug resistance has decreased over calendar time. Moderate evidence of an association between TDR and acute infection may suggest TDR impacts SC illness or that we underestimate TDR if not tested immediately following SC. Our study provides a realistic estimate about the temporal trend of TDR due to inclusion of individuals with recent infection.

603 Increase in HIV Primary Drug Resistance in a Demographic Surveillance Area in Rural KwaZulu-Natal South Africa

Justen Manasa; Siva Danaviah; Frank Tanser; Sureshnee Pillay; Hloniphile Mthiyane; Eduan Wilkinson; Deenan Pillay; **Tulio de Oliveira**
University of KwaZulu-Natal, Durban, South Africa

Background: Increased access to antiretroviral therapy (ART) has been associated with significant reductions in AIDS related morbidity and mortality as well as a significant reduction in HIV incidence. As more patients access ART, higher proportions of newly infected patients is expected to be infected with drug resistant viruses in resource limited settings.

Methods: Samples from treatment naïve participants from 3 rounds of an annual population based HIV surveillance programme in rural Kwazulu-Natal were genotyped for drug resistance. The sample types included, EDTA microtubes (2010) and DBS (2011 and 2012). Samples were selected from the population for 2010, 2011 and 2012 with an estimated duration of infection. In addition, we randomly selected samples from chronically infected drug naive individuals with VL > 10,000 copies/ml (2011 and 2012). The quality of sequences was assessed using the Calibrated Population Resistance (CPR) tool and by phylogenetic reconstruction analysis using ML and NJ methods. The 2009 surveillance of drug resistance mutation (SDRM) list was used in the drug resistance analysis. All statistical analyses were undertaken using Stata 10.

Results: We sequenced 701 treatment naïve individuals (success rate 86%); 67 (2010), 381(2011), and 253 (2012). This represents approximately 15% of the surveillance samples for 2011 and 2012. Men constituted 25% of the participants. The average age was 34 years and the median viral load was 116,600 RNA copies/ml. One or more SDRM were identified in 36 (5%) of the 701 participants. Of these, the NNRTI SDRM were the most dominant, being detected in 32 (5%) samples. The most common were K103N, V106M and G190A, in 27 (3.8%), 3 (0.4%) and 2 (0.3%) samples respectively. Only 3 (0.4%) samples had 2 or more NNRTI SDRM. NRTI SDRM were detected in 11 (1.6%) of the participants, 9 of whom had only one NRTI SDRM. Six (1%) of the participants had both NNRTI and NRTI resistance mutations, K103N + M184V being the most common combination. There was no evidence of SDRM from the 2010 participants. The 2011 and 2012 samples both had 18 participants with some SDRM, 5% and 8% respectively.

Conclusions: The NNRTI SDRMs are the major contributors to observed patterns of primary drug resistance. There is an increasing need to identify recently infected participants in order to better understand the trends in primary drug resistance in reponse to changes in treatment coverage and treatment regimens in public sector treatment programmes.

THURSDAY, FEBRUARY 26, 2015

Session P-L4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HIV Drug Resistance: Global Perspective and Clinical Implications

604 A Clinical Prediction Rule for PI Resistance in Resource-Limited Settings

Karen Cohen[1]; Annemie Stewart[1]; Andre P. Kengne[1]; Rory F. Leisegang[1]; Marla Coetsee[2]; Shavani Maharaj[2]; Liezl Dunn[2]; Graeme Meintjes; Gert U. van Zyl[3]; Gary Maartens[1]

[1]*University of Cape Town, Cape Town, South Africa;* [2]*Aid for AIDS Management (Pty) Ltd, Cape Town, South Africa;* [3]*University of Stellenbosch, Cape Town, South Africa*

Background: Although virological failure is common in adults on second-line ART in resource limited settings, major protease inhibitor (PI) resistance mutations occur infrequently. Therefore, empiric switches to salvage therapy would waste resources. Resistance testing identifies patients needing salvage therapy, but is expensive and access is limited. Therefore, a clinical prediction rule (CPR) to rationalise access to resistance testing would be a valuable tool.

Methods: We identified predictors of major PI resistance mutations in a large South African cohort. We included adults with virological failure and ≥ 4 months exposure to lopinavir/atazanavir-based ART. PI resistance was defined as ≥1 major resistance mutations to current PI. We constructed a multivariate logistic regression model including age, sex, PI duration, adherence by pharmacy claims, concomitant CYP3A4-inducing drugs and viral load (VL) at time of genotyping as candidate predictors based on an *a priori* decision. We selected variables included in the CPR using a stepwise approach. We internally validated by bootstrapping. We categorised included variables, and assigned points to each level based on adjusted beta coefficients.

Results: There was PI resistance in 146/339 (43%) patients. Median age was 42 years (IQR 36 to 47), 211 (62%) were female, and 309 (91%) and 30 (9%) were on ritonavir-boosted lopinavir and atazanavir respectively. Median PI duration was 2.6 years (IQR 1.6 to 4.7). Median adherence was 97% (IQR 73 to 100) and 9% took concomitant inducing drugs. Median log VL was 4.9 (IQR 4.3 to 5.4).

Presence of major PI resistance mutations were associated with age (adjusted odds ratio (aOR) for 10 year increase 1.9 (95% CI 1.4 to 2.6)); PI duration (aOR per year 1.1 (95% CI 1.0 to 1.3)); and adherence (aOR per 10% increase 1.2 (95% CI 1.1 to 1.3)). There was no association with sex, inducer exposure and VL. We included age, PI duration and adherence in the CPR.

Area under the ROC curve was 0.736 (95% CI 0.683 to 0.789) before and 0.739 (95% CI 0.736 to 0.742) after bootstrapping. The model had acceptable calibration. The optimal cut point corresponded to a score of 8/15 (75% sensitivity and 67% specificity).

Clinical prediction rule for major PI resistance mutations

Risk factor category	Points assigned	Score	Predicted probability (%)	Sensitivity	Specificity
Age in years					
18 to 29	0	0-2	≤8.6	100%	≤2%
30-39	2	3	11.8	99%	8%
40-49	4	4	15.8	99%	12%
50-59	6	5	20.9	98%	19%
60-65	8	6	27.2	94%	31%
Duration on PI		7	34.5	82%	48%
4m-2 years	0	8	42.6	75%	67%
2-4 years	1	9	51.1	60%	75%
5-11 years	3	10	59.6	38%	85%
Adherence last 4 months		11	67.5	32%	90%
0-39%	0	12	74.6	5%	98%
40-60%	2	13	80.5	5%	98%
60-80%	3	14-15	≥85.4	≤1%	100%
80-100%	4				

Table: Clinical prediction rule for major PI resistance mutations

Conclusions: Older patients with high adherence and prolonged PI exposure are most likely to benefit from resistance testing. The CPR may be a useful tool to rationalise patient selection for resistance testing in resource limited settings, but requires external validation

605 Baseline Low-Frequency HIV-1 Variants Do Not Predict Virologic Failure to RPV/FTC/TDF

Danielle P. Porter[1]; Martin Däumer[2]; Alexander Thielen[2]; Michael D. Miller[1]; Kirsten L. White[1]

[1]*Gilead Sciences, Inc., Foster City, CA, US;* [2]*Seq-IT GmbH & Co KG, Kaiserslautern, Germany*

Background: Rilpivirine/emtricitabine/tenofovir DF (RPV/FTC/TDF) is currently approved for use in HIV-1 treatment-naïve adults with HIV-1 RNA ≤100,000 c/mL due to increased virologic failure with resistance development in patients with high baseline viral load (BL VL). At Week 96 in the phase 3b STaR study (GS-US-264-0110; RPV/FTC/TDF vs. efavirenz/FTC/TDF in treatment-naïve adults with no BL VL restriction), 5.3% of patients on RPV/FTC/TDF developed resistance mutations by population sequencing (9.0% BL VL >100,000 c/mL vs. 3.5% BL VL ≤100,000 c/mL). Deep sequencing was performed to assess the potential clinical impact of pre-existing minority variants in RPV/FTC/TDF-treated patients with high BL VL.

Methods: Deep sequencing (Illumina MiSeq) was performed on baseline and virologic failure (VF) samples for 24 RPV/FTC/TDF-treated patients in the resistance analysis population (RAP; patients with HIV-1 RNA ≥400 c/mL at VF, discontinuation, or Weeks 48 or 96). Baseline samples from 44 non-RAP RPV/FTC/TDF-treated BL VL and BL CD4 matched control patients, including all 29 with BL VL ≥500,000 c/mL, were also analyzed. Deep sequencing results (≥1% cutoff) were compared to population sequencing.

Results: Baseline NRTI- or NNRTI-associated mutations were detected in 29% (7/24) of RAP isolates and 27% (12/44) of controls by deep sequencing. Study exclusion mutations were detected at low frequencies in 4 RAP patients (BL VL >100,000 c/mL: E138K, H221Y n=1 each; BL VL ≤100,000 c/mL: M184V, E138G n=1 each). While all 4 patients developed NRTI- and/or NNRTI-associated mutations in their HIV-1 at VF, none of these same mutations were detected except for 1 patient with 1.17% M184V at baseline who had >99%

M184V at VF. Exclusion mutations were also detected at low frequencies in 7 control patients (BL VL >100,000 c/mL: K65R, E138K n=2 each; Y181C, E138G n=1 each; BL VL ≤100,000 c/mL: E138G n=1). Six were virologic successes at Week 96; 1 patient with 1.08% K65R discontinued at Week 32 with HIV-1 RNA 64 c/mL. Additional NRTI- or NNRTI-associated mutations not detected by population sequencing at VF were detected in 41% (9/22) of RAP VF isolates with deep sequencing data.

Conclusions: The presence of low-frequency NRTI- and NNRTI-associated mutations at baseline was not predictive for VF or resistance development for RPV/FTC/TDF-treated patients in the STaR study. Deep sequencing results were generally consistent with population sequencing but detected additional low-frequency resistance mutations at VF.

606 High Rates of Early Virologic Failure in a Cohort of Tanzanian HIV-Infected Adults

Claudia A. Hawkins[1]; Nzovu Ulenga[2]; Enju Liu[3]; Said Aboud[4]; Ferdinand Mugusi[4]; Guerino Chalamilla[2]; David Sando[2]; Eric Aris[2]; Wafaie Fawzi[3]

[1]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [2]Management and Development for Health, Dar es Salaam, United Republic of Tanzania; [3]Harvard School of Public Health, Boston, MA, US; [4]Muhimbili University of Health and Allied Sciences, Dar es Salaam, United Republic of Tanzania

Background: There are few data on antiretroviral treatment (ART) failure and HIV drug resistance in Tanzania where there are a wide diversity of non-B HIV subtypes. We assessed rates and risk factors associated with virologic failure (VF) in a cohort of Tanzanian HIV-infected adults on first line antiretroviral therapy (ART) and describe resistance patterns in a subset of patients.

Methods: Non-pregnant, ART naïve, HIV-1 infected adults who were enrolled in a randomized controlled multivitamins trial between November 2006 -2008, and on at least 24 weeks first-line NNRTI-containing ART were included in the analysis. Population-based genotyping (GT) of HIV-1 protease and reverse transcriptase was performed on plasma samples from patients with VF, defined as a viral load (VL) ≥1000 copies/mL at ≥24 weeks of ART, where available. Log-binomial regression models were used to examine predictors of virologic failure.

Results: 2,403 HIV-infected adults (median age 37 (IQR 32,43); 70% female) were included in the study. Median baseline CD4+ T cell count was 128 (IQR 62,190) cells/mm^3 and 76% were WHO stage III or IV. The combination of d4T, 3TC and NVP or AZT, 3TC and EFV was used in 82%. Median time on ART was 10.3 (IQR 7.5,11.9) months. Subtype distribution (n=64) was A (17, 27%), B (1,2%), C (24, 37%), CRF01_AE (4, 6%), and D (18, 28%). The overall rate of VF was 14.9% (IQR 13.2%, 16.1%). In multivariate analyses, significant predictors of VF were lower CD4+ T cell counts, [RRs 1.4 (95%CI 0.9-1.9), 1.6 (1.1-2.2), 1.2 (0.8-1.6) for patients with CD4<50, 50-<100, 100-<200 cells/mm^3 vs. CD4≥200 cells/mm^3 respectively, (p for trend=0.01)], and visit non-adherence [RR 1.5 (1.1, 1.9), p<0.01]. GT was performed on 115 samples from 106 patients with VF. Drug resistance mutations (DRMs) were present in 87/115 (75.7%). The most common drug resistance mutations (DRMs) were M184V/I (60/115, 52%), K103N (40/115, 35%), Y181C/I (29/115, 25%), G190A/S (20/115,17%). At least one Thymidine Analog Mutation (TAM) was present in 6/115 (5%). DRMs (≥1) conferring potential resistance to etravirine were present in 6%. K65R was present in 2 patients.

Conclusions: High levels of early ART failure and DRMs were observed in this Tanzanian cohort of HIV-1 infected patients enrolled in a well-monitored study setting, reinforcing the importance of routine VL testing. Early initiation of ART and optimal adherence early on in therapy is crucial for the success of commonly used first line therapies in sub-Saharan Africa.

607 HIV Drug Resistance Surveillance in Honduras After 10 Years of Widespread ART

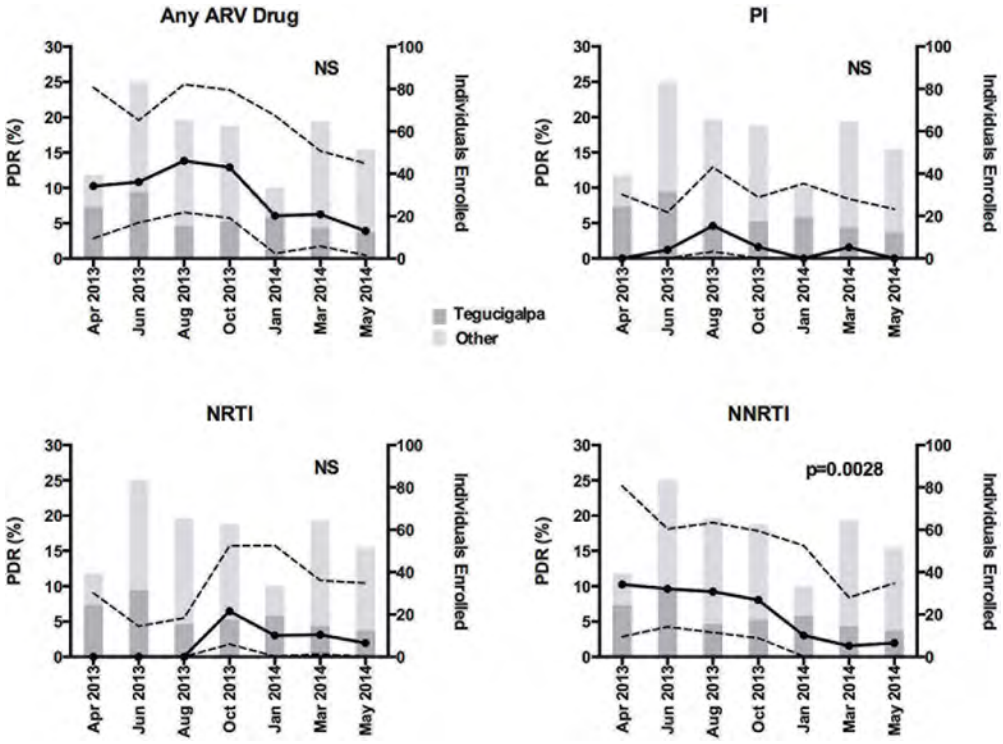
Claudia Garcia-Morales[1]; **Santiago Avila-Rios**[1]; Daniela Tapia-Trejo[1]; Rita Meza[2]; Sandra Nuñez-Rubio[2]; Norma Flores[5]; Wendy Murillo[3]; Ivette Lorenzana[3]; Elsa Palou[4]; Gustavo Reyes-Terán[1]

[1]National Institute of Respiratory Diseases, Mexico City, Mexico; [2]Honduran HIV National Program and National Laboratory, Tegucigalpa, Honduras; [3]Universidad Nacional Autónoma de Honduras, Tegucigalpa, Honduras; [4]Hospital Escuela Universitario, Tegucigalpa, Honduras; [5]Instituto Nacional Cardiopulmonar, Tegucigalpa, Honduras

Background: HIV drug resistance (DR) surveillance is key to maximizing the long-term effectiveness of antiretroviral treatment (ART) regimens and to ensure the sustainability of ART programs. We present results from a national study to assess the prevalence and trends of HIVDR in individuals failing ART (acquired DR, ADR) and in ART-naïve individuals (pre-ART DR, PDR) in Honduras, after 10 years of widespread availability of ART.

Methods: 294 HIV-infected, ART-naïve, and 316 ART-experienced Honduran individuals were enrolled in 5 reference centers in Tegucigalpa, San Pedro Sula, Choluteca and La Ceiba, between April 2013 and July 2014. Plasma HIV protease-RT sequences were obtained. HIVDR was assessed using the WHO HIV transmitted DR (TDR) surveillance mutation list and the Stanford algorithm (v7.0). Recently infected (RI) individuals were identified using a multiassay algorithm using incidence tests, in order to assess TDR.

Results: PDR to any ARV drug was 9.9%. NNRTI PDR prevalence (6.5%) was higher than NRTI (2.0%) and PI (2.0%, p<0.0001). A decrease in NNRTI PDR was observed comparing 2013 and 2014 (p=0.0234). This observation was confirmed using a moving average approach (p=0.0028), and was consistent with lower, although not significant, NNRTI TDR in RI individuals (4.8%). The most prevalent PDR mutations were M46IL (1.7%) to PI, T215X (0.7%) to NRTI, and K103NS (4.4%) to NNRTI. E138X mutations, conferring DR to rilpivirine were also highly prevalent (4.4%), causing higher PDR estimations when using the Stanford DR definition (15.6% to any ARV drug). The overall ADR prevalence for individuals with <48 months on ART was 88.0% and for the ≥48 months on ART group 79.8%. In both cases, PI ADR was lower, compared with NRTI and NNRTI (p<0.0001). ADR to two drug families was 71.1% and 67.0% and ADR to three drug families 1.2 and 9.9% respectively, with an increase in PI ADR in individuals with longer time on ART. M184V (67.0%), and K103N (40.3%) were highly frequent. PDR mutation frequency correlated with ADR mutation frequency both in individuals with <48 and ≥48 months on ART for PI and NNRTI (p<0.0005 in all cases), but not for NRTI.



HIV PDR trends in Honduras 2013-2014. PDR trends by date of enrolment were estimated using a moving average approach, with 3-month windows, moving by 2-month intervals. TDR prevalence and 95% confidence intervals (CI) are shown. The number of individuals enrolled for each estimation is shown: dark gray, individuals coming from Tegucigalpa; light gray, individuals coming from other parts of the country. PDR, pre-antiretroviral treatment drug resistance; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

Conclusions: The global PDR prevalence in Honduras remains at the intermediate level, after 10 years of widespread availability of ART with PDR mutation frequency being highly influenced by ADR mutation frequency. Decreasing trends were observed for NNRTI PDR, which will have to be confirmed by periodic HIVDR surveillance.

608 High Prevalence of Genotypic Resistance to Integrase inhibitors of HIV-1 Strains in Taiwan

Sui-Yuan Chang[1]; Chien-Ching Hung[2]

[1]National Taiwan University, Taipei, Taiwan; [2]National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

Background: Integrase inhibitor in combination with 2 nucleoside reverse-transcriptase inhibitors has been shown to be effective treatment options for antiretroviral(ARV)-naive HIV-1-infected patients. In Taiwan, raltegravir was first introduced in 2009 as a regimen of second line ARV and a pilot study by our laboratory in 2011 revealed that there was no HIV-1 strains harboring integrase inhibitor-related major genetic mutations among the 160 analyzed specimens from treatment-naive patients. In this study, we aimed to determine the prevalence of integrase inhibitor-related genetic mutations after the implementation of regulations on the prescription of HAART to ARV-naive patients by the Taiwan Centers of Disease Control (CDC) on 1 June 2012, by which raltegravir can only be used in combination with zidovudine/lamivudine in ARV-naive patients or with other ARVs in treatment-experienced patients.

Methods: Genotypic resistance assays were performed in the HIV strains from ARV-naïve patients seeking HIV care at the designated hospitals around Taiwan from June 2012 to December 2013. Resistance mutations to integrase inhibitors were identied using the HIVdb program of the Stanford University HIV Drug Resistance Database. Phylogenetic tree was constructed to determine the relationship between the resistant strains identified.

Results: Of the 1087 HIV-1 strains included for analysis, the majority were subtype B (82.9%) and CRF01_AE (6.5%). The overall prevalence of TDR to integrase inhibitors was 6.0% (n=65), which includes 56 HIV-1 strains of subtype B, 5 CRF01_AE and 4 CRF07_BC. The prevalence of TDR to integrase inhibitors increased from 6.8% in the third quarter of 2012, peaked at 9.4% in the first quarter of 2013, and gradually declined to 3.3% in the last quarter of 2013. Among the identified II-related genetic mutations, Q148K and N155S were found in 41.5% (n=27) and 29.2% (19) of the integrase inhibitor-resistant strains, respectively. Other mutations identified include T66A (n=2), E92Q/KV (9), E138K (2), Y143C/R/S (5), P145R (4), E157Q (4), and R263K (3). Phylogenetic analysis showed that there was no clustering observed among these resistant sequences.

Conclusions: In Taiwan, the prevalence of TDR to integrase inhibitors recently increased to 6.0%, which was temporally related to the implementation of regulations on the use of antiretroviral drugs in ARV-naïve patients.

609 Integrase Resistance Correlates of Response to Dolutegravir (DTG) Through 48 Weeks

Cindy L. Vavro; Jenny Huang; Mounir Ait-Khaled

GlaxoSmithKline, Research Triangle Park, NC, US

Background: Phenotypic and genotypic correlates of antiviral response (AR) derived from clinical investigation characterize an antiretroviral's (ART) ability to inhibit HIV. The VIKING-3 and VIKING-4 (V3/4) studies examined DTG 50mg twice-daily in patients with resistance to multiple ART's, including integrase inhibitors (INI). Baseline Integrase (IN) genotypes and phenotypes were assessed to identify correlates to AR.

Methods: In both studies DTG 50mg BID was given through Day 8 as functional monotherapy followed by optimization of background regimen. V3 data only was used for deriving correlates to AR. Day 8 categories for AR as change from Baseline in HIV-1 RNA were pre-defined as Full (>1.0 $\log_{10}$), Intermediate (0.5-1.0 $\log_{10}$) or No response (<0.5 $\log_{10}$). IN resistance tests were performed by Monogram BioSciences. Baseline DTG fold change (FC) phenotypic cut-offs for Day 8 AR were examined using non-linear logistic regression modeling. For IN genotypic correlates, incidence of resistance-associated mutations and co-incidence of mutation pairs at Baseline were examined. Multivariate logistic regression

analyses of genotypic data were performed to identify Baseline IN mutations impacting Day 8 AR. Derived IN resistance correlates were tested on Week 24 and Week 48 AR (ITT-E, %<50 c/mL, 'Snapshot') using combined V3/4 AR data (N=213).

Results: At Day 8, no definite DTG FC cut-offs for No AR and Full AR were identified due to limited numbers of non-responders and few viruses with high DTG FC. A high correlation between mutations at position G140 and Q148 was confirmed (P <0.001). Three Baseline IN resistance mutation groups were identified as predictors of Day 8 AR which remained associated with response at Weeks 24 and 48 in V3: No Q148 (includes Y143, N155, T66, E92 and virus with only historic IN primary mutations), Q148+1 and Q148+2 (of one or two or more of specific secondary mutations G140A/C/S, L74I, or E138A/K/T). Integrated V3/4 Week 24 AR rates by these derived mutation groups were 78%, 52%, and 24%, respectively; a similar AR pattern was seen at Week 48 with 70%, 48%, and 28%(ITT-E, % <50c/mL by Snapshot).

Conclusions: The three derived baseline IN genotypic groups (No Q148 mutations, Q148 +1, and Q148 +2) were good predictors for DTG responses through Week 48, and thus provide guidance for the clinical use of DTG in patients with INI-resistant virus. Response rates were maintained between Week 24 and 48 for all three IN genotypic groups.

610 Discordant Predictions Could Impact Dolutegravir Use Upon Raltegravir Failure

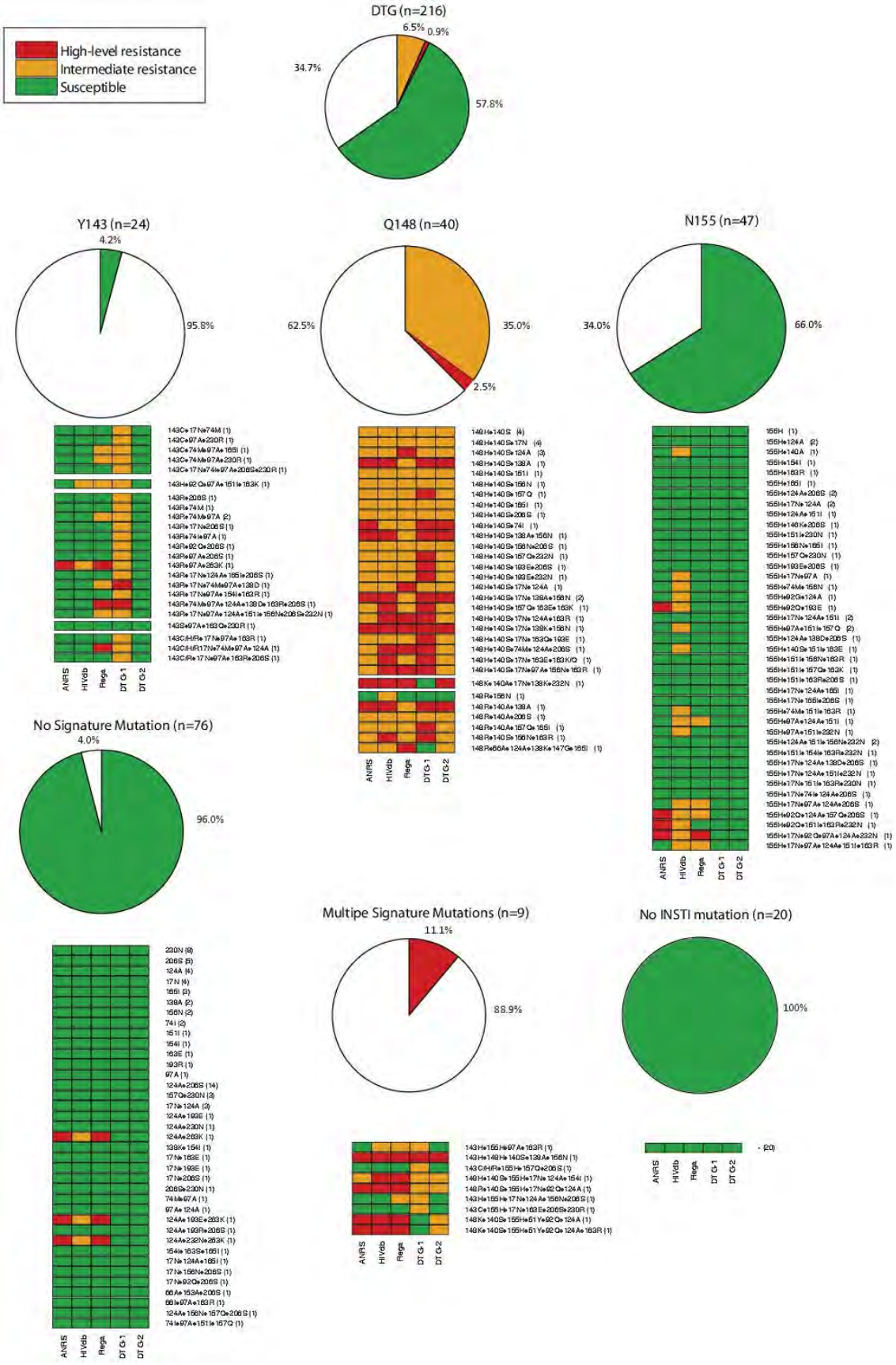
Kristof Theys[1]; Ana B. Abecasis[2]; Pieter Libin[1]; Perpétua Gomes[2]; Joaquim Cabanas[3]; Ricardo J. Camacho[1]; Kristel Van Laethem[1]
the Portuguese HIV-1 Resistance Study Group
[1]*University of Leuven, Leuven, Belgium;* [2]*Universidade Nova de Lisboa, Lisbon, Portugal;* [3]*Hospital Egas Moniz, Lisbon, Portugal*

Background: The latest integrase strand transfer inhibitor (INSTI) dolutegravir (DTG) has been approved for HIV-1 patients with resistance to INSTIs raltegravir (RAL) and elvitegravir (EVG). While expanding therapeutic options, the decision for DTG use in this setting should be informed by the presence of baseline mutational patterns.

Methods: Integrase sequences of 216 HIV-1 infected patients failing therapy containing RAL were collected. An exhaustive list of INSTI resistance-associated mutations (RAMs) was defined based on the IAS-USA 2013 list, resistance interpretation systems ANRS v23, HIVdb v7.0 and Rega v9.1.0, and on FDA and EMA package inserts of RAL, EVG and DTG. Mutation patterns were categorized into resistance levels scored by ANRS, HIVdb, Rega, and two additional categorization schemes (DTG-1 and DTG-2) derived from FDA and EMA package inserts.

Results: One or more INSTI RAMs was observed in 188 patients (87%), with 43 of 79 defined RAMs detected and a major INSTI RAM present in 132 patients (62%). The most prevalent RAL signature mutations were N155H (25.4%), Q148H (16.2%) and Y143R (8.3%). Predictied RAL activity upon failure displayed low levels of discordance (8.8%), and concordant scores were mainly high-level resistant (R) (52.3%) or susceptible (S) (36.6%), and less intermediate resistant (IR) (2.3%). The majority of patients were still concordantly scored susceptible to DTG (57.8%). A total of 141 unique INSTI mutational patterns were classified into 6 groups according to mutations at signature positions 143, 148 and 155. A signature mutation was not detected in 96 patients (44%), of which 97% was concordantly scored susceptible, whereas patients displaying the N155H pathway (21.88%) showed concordant susceptible scores in 66% of patients. Patients harboring the Q148 pathway (18.5%) were concordantly scored (I)R in 37.5%. Nevertheless, disagreement between all five systems occurred for 34.7% of patients. Although concordant (I)R DTG scores were only obtained in 7.4% of patients, individual interpretation systems scored (I) R more often, from 20.4% for DTG-2 to 31% for HIVdb and DTG-1. Highest levels of discordance were observed for Y143 (95.8%) and Q148 (62.5%) pathways and for patterns of multiple signature mutations (88.9%).

Conclusions: DTG may potentially be effective in most HIV-1 patients failing RAL. However, a consensus on interpreting the extent of residual activity is highly resistance pathway specific, which could lead to uncertainty in individual patient management.



Concordant and discordant dolutegravir (DTG) resistance scores in HIV-1 sequences obtained after raltegravir (RAL) failure, interpreted with rules derived from ANRS v23, HIVdb v7.0, Rega v9.1.0, FDA and EMA package inserts, as defined in methodology section. The number of unique mutational patterns are displayed and categorized according to the presence of Y143CHRS, Q148HKR and/or N155H. Concordant susceptible [green], intermediate resistant [orange], resistant [red] and discordant [white] scores.

611 Integrase S119P Mutation Correlates With Disease Progression in HIV-1 Naïve Patients

Daniele Armenia[1]; Maria Mercedes Santoro[1]; Caterina Gori[2]; Emanuele Nicastri[2]; Antonio Cristaudo[3]; Massimo Andreoni[4]; Andrea Antinori[2]; Zeger Debyser[5]; Carlo-Federico Perno[2]; Francesca Ceccherini-Silberstein[1]

[1]University of Rome Tor Vergata, Rome, Italy; [2]L. Spallanzani Hospital, Rome, Italy; [3]San Gallicano Dermatological Institute, Rome, Italy; [4]University Hospital Tor Vergata, Rome, Italy; [5]Katholieke Universiteit Leuven, Leuven, Belgium

Background: Recent finding showed that specific HIV integrase (IN) polymorphisms at positions S119, T122 and R231 affect integration site targeting in the host genome. Moreover, mutations at position S119 have been associated with HLA selection. We thus characterized the prevalence of IN polymorphisms at these positions and their association with CD4 cell count and HIV-RNA in HIV-1 infected HAART-naïve patients.

Methods: The association between IN polymorphisms at position S119, T122 and R231 with CD4 count and HIV-RNA has been evaluated in a cohort of HAART-naïve patients with IN genotypic resistance test (GRT). In patients with at least 2 HIV-RNA/CD4 measurements before HAART start, survival analyses were used to evaluate the event of starting HAART or to reach a CD4 cell count <350 cells/μl.

Results: 625 patients, mainly HIV-1 subtype B infected (B: 71.2%; CRF_02AG: 7.2%, F: 6.6%, C: 3.7%, other subtypes: 11.3%) have been enrolled. The following IN polymorphisms were found: at position 119, P (19.2%), G (9.0%) and A/R/T (8.7%); at position 122, I (20.8%) and S/V (2.1%); at position 231, K (1.8%).

One hundred sixty-nine patients, with available follow-up before treatment start (median [IQR] time: 13.1 [5.5-24.1] months) were longitudinally analysed. Baseline CD4 count and HIV-RNA were 458 (IQR: 376-600) cells/μl and 4.6 (IQR: 4.1-5.0) $\log_{10}$cps/mL, respectively. At baseline, no significant associations between polymorphisms at positions 119/122/231 with CD4 count and HIV-RNA were found. The median [95% CI] time of starting HAART or to reach a CD4 count <350 cell/μl was 15.8 [12.8-18.6] months. Interestingly, patients with 119P mutation showed a shorter time to reach the end-point compared to those with G or S_{wt} residues (9.3 [5.6-13.0] vs. 14.7 [9.4-20.0] vs. 16.8 [14.0-19.7] months, p=0.020). Cox multivariable analyses (adjusting for age, gender, subtype, baseline CD4 and HIV-RNA) confirmed that, among all polymorphisms found at positions 119/122/231, only S119P had a higher hazard to achieve the event compared to those with $119S_{wt}$ (RH [95 CI%]: 2.0 [1.2-3.2], p=0.006).

Conclusions: IN position S119, beyond the observed correlations with integration site targeting and host immune response, might define patients with accelerated disease progression. Further investigations on polymorphisms at position S119 are necessary to understand our observation.

TUESDAY, FEBRUARY 24, 2015

Session P-M1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Nucleic-Acid–Based Detection of HIV

612 A Generalized Entropy Measure of Viral Diversity for Identifying Recent HIV-1 Infections

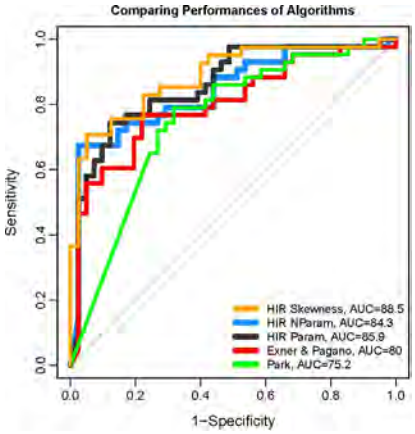
Julia W. Wu; Oscar Patterson-Lomba; Marcello Pagano

Harvard School of Public Health, Boston, MA, US

Background: There is a need for incidence assays that accurately estimate HIV incidence based on cross-sectional specimens. Viral diversity-based assays have shown promises but are not particularly accurate. We hypothesize that certain viral genetic segments are more predictive of recent infection than others and aim to improve assay accuracy by employing classification algorithms that focus on the highly informative regions (HIR).

Methods: We analyzed HIV *gag* sequences from a cohort in Botswana. Forty-two subjects newly infected by HIV-1 Subtype C were followed longitudinally through 500 days post-seroconversion. Using sliding window analysis, we screened for genetic segments within *gag* that best differentiate acute versus chronic infection. We used both non-parametric and parametric approaches to evaluate the discriminatory abilities of sequence segments. Segmented Shannon Entropy measures on HIRs were aggregated to develop generalized entropy measures to improve prediction of recency, defined as infection within past 6 months. With logistic regression as the basis for our classification algorithm, we evaluated the predictive power of these novel biomarkers and compared them with recently reported viral diversity measures using Area under the Curve (AUC) analysis. To further improve prediction, we also explored other diversity-related biomarkers.

Results: Change of diversity over time varied across different sequence segments within *gag*. The top 50% most informative segments were identified through non-parametric and parametric approaches. In both cases HIRs were in non-flanking regions and less likely in the *p24* coding region. These new indices outperformed previously reported viral-diversity-based biomarkers. Including skewness in the assay further improved the AUC (see Figure 1), whereas other existing methods did not add much additional predictive power. Sensitivity analysis suggests that antiretroviral use had little impact on our assay performances. We also demonstrate that sensitivity and specificity depend on the datasets used and the underlying distributions of time-since-infection. This explains why we obtained different AUC values compared to previous studies.



Comparing predictive performances of different algorithms.

Conclusions: Our generalized entropy measure of viral diversity demonstrates the potential for improving accuracy when identifying recent HIV-1 infections. We also show that to properly compare and evaluate assay performances, the distribution of time-since-infection in the validation dataset needs to be accounted for.

613 Acute Infections, Cost and Time to Reporting of HIV Test Results in US State Public Health Laboratories

Muazzam Nasrullah[1]; Laura G. Wesolowski[1]; Steven F. Ethridge[1]; Kevin Cranston[2]; Robert A. Myers[3]; James T. Rudrik[4]; Angela B. Hutchinson[1]; Barbara G. Werner[2]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]Massachusetts Department of Public Health, Boston, MA, US; [3]Maryland Department of Health and Mental Hygiene, Baltimore, MD, US; [4]Michigan Department of Community Health, Lansing, MI, US

Background: In 2014, CDC recommended an HIV diagnostic algorithm (repeatedly reactive [RR] 4th-generation immunoassay [IA] that detects HIV-1 antigen and HIV antibody, followed by an HIV-1/HIV-2 differentiation antibody IA, and when negative or indeterminate, an HIV-1 nucleic acid test [NAT]) to detect acute infections and to reduce misclassification of HIV-2 as HIV-1 infections. In three U.S. state public health laboratories (PHLs), we characterized the yield of acute infections, time to reporting of acute and antibody-positive HIV-1 infections, and cost per positive specimen.

Methods: Routine HIV testing data were collected from 7/1/2012- 6/30/2013 for Massachusetts (MA) and Maryland (MD) PHLs, and from 11/27/12- 6/30/2013 for Michigan (MI) PHL. MA and MI used the CDC algorithm with NAT conducted by a referral laboratory, and MD used a modified algorithm. In MD PHL, 4th-generation IA RR specimens were followed by Western Blot (WB), and those with negative or indeterminate WB results were tested with an HIV-1/HIV-2 differentiation IA and an HIV-1 NAT, and if positive by NAT, confirmed by a different HIV-1 NAT. HIV-2 positive specimens on an HIV-1/HIV-2 differentiation IA were tested with HIV-2 WB and differential HIV-1/HIV-2 proviral DNA polymerase chain reaction (PCR). In each PHL, we determined the time from specimen receipt to laboratory reporting of test results, and total testing and labor costs per HIV positive (HIV-1 and HIV-2).

Results: Among 7,914 specimens from MA PHL, 6,069 from MI PHL and 36,266 from MD PHL, 8, 1 and 19 acute infections were identified, respectively (Table). For MA and MD PHL, 1 specimen each was identified as HIV-2 positive. The median time from specimen receipt to laboratory reporting of test results for acute infections was 7, 11 and 7 days and for HIV-1 antibody-confirmed infections was 3, 2 and 3 days, respectively. The cost per HIV positive specimen was $336 in MA PHL, $281 in MI PHL and $221 in MD PHL.

Table: Results of 4th generation immunoassay HIV testing data among the U.S. State Public Health Laboratories.

	Massachusetts State Public Health Laboratory, Boston MA	Michigan State Public Health Laboratory, Lansing MI	Maryland State Public Health Laboratory, Baltimore MD
Fourth-generation immunoassay	Bio-Rad GS HIV Antigen/Antibody Combo	Bio-Rad GS HIV Antigen/Antibody Combo	Abbott Architect HIV Antigen/Antibody Combo
Prospective time period immunoassay test results	7/1/2012- 6/30/2013	11/27/12- 6/30/2013	7/1/2012- 6/30/2013
Total	7914	6069	36266
Non-reactive	7652 (96.69%)	5898 (97.18%)	35232 (97.15%)
Repeatedly reactive	262	171	1034
Results of repeatedly reactive immunoassays			
Confirmed HIV-1 antibody positive[a]	246 (3.11%)	163 (2.68%)	983 (2.71%)
Acute infection[b]	8 (0.10%)	1 (0.02%)	19 (0.05%)
IA false positive[c]	7 (0.09%)	5 (0.08%)	29 (0.08%)
HIV-2 positive[d]	1 (0.01%)	0 (0.00%)	1 (0.003%)
Incomplete testing	0 (0.00%)	0 (0.00%)	0 (0.00%)
Other	0 (0.00%)	2 (0.03%)[e]	2 (0.005%)[f]

[a] HIV-1 positive by Western blot (WB) or HIV-1/HIV-2 antibody test
[b] 4th generation immunoassay (IA) repeatedly reactive, WB or HIV-1/HIV-2 differentiation IA negative or indeterminate, detectable nucleic acid test (NAT)
[c] 4th generation IA repeatedly reactive, WB or HIV-1/HIV-2 differentiation IA negative or indeterminate, NAT not detected
[d] Positive for HIV-2 by HIV-1/HIV-2 differentiation IA or HIV-2 WB or differential HIV-1/HIV-2 proviral DNA conventional polymerase chain reaction
[e] IA repeatedly reactive, HIV-1/HIV-2 differentiation IA undifferentiated, WB positive, NAT not detected (n=1); IA repeatedly reactive, HIV-1/HIV-2 differentiation IA undifferentiated, NAT not detected (n=1)
[f] IA repeatedly reactive, WB indeterminate, HIV-1/HIV-2 differentiation IA positive, NAT not detected (n=1); IA repeatedly reactive, WB indeterminate, HIV-1/HIV-2 differentiation IA negative, NAT not detected (n=1)

Conclusions: Fourth-generation IA, coupled with antibody tests and NAT, detected acute infections in PHLs that may have been missed if an antibody-only test such as the Western Blot had been used as a confirmatory test. Promotion of the CDC HIV testing algorithm, with quicker reporting of acute infections, will facilitate public health intervention to interrupt transmission.

614 The POC Alere q HIV-1/2 Detect Test for Detection and Quantification of HIV-2

Ming Chang[1]; Katja Weimar[2]; Dana N. Raugi[1]; Robert A. Smith[1]; Selly Ba[3]; Moussa Seydi[3]; Katrin Steinmetzer[2]; Robert W. Coombs[1]; **Geoffrey S. Gottlieb**[1]
UW-Dakar HIV-2 Study Group

[1]University of Washington, Seattle, WA, US; [2]Alere Technologies GmbH, Jena, Germany; [3]Service des Maladies Infectieuses, CHNU de Fann, Dakar, Senegal

Background: Rapid point-of-care (POC) nucleic acid testing (NAT) that can detect, differentiate and quantify HIV-1 and HIV-2 RNA/DNA has the potential to improve the cascade of care and antiretroviral therapy monitoring. In addition, the new 4th-generation CDC algorithm for HIV diagnostic testing specifies differential HIV-1 and HIV-2 serologic and nucleic acid testing, but there are no FDA-approved confirmatory HIV-2 NAT assays currently available.

Methods: We compared the ability of the Alere q HIV-1/2 Detect test with 25μL of sample input and the recently-validated University of Washington (UW)-Abbott m2000 HIV-2 viral load assay to detect and differentiate between HIV-1 and HIV-2. Under a "research use only" protocol, the Alere q HIV-1/2 platform was used to quantify HIV-2 plasma RNA viral load. Clinical samples from HIV-2 and HIV-1/2 dually-infected patients from Senegal were tested, along with the WHO HIV-2 international standard and HIV-2 reference strains. All testing was performed in the CLIA-certified UW Clinical Retrovirology Lab.

Results: The Alere HIV-1/2 Detect test correctly differentiated HIV-1 from HIV-2 in 100% of 77 patient samples tested (N=17 HIV-1, 60 HIV-2) and detected HIV-2 nucleic acids in 56 of 118 (47%) plasma samples from HIV-2–infected individuals. The Alere test detected HIV-2 in group A and group B specimens, as well as the WHO international standard ($HIV\text{-}2_{CAM2}$; group A) and other reference isolates. The overall concordance between the Alere test and the Abbott m2000 assay was 56/82 (68%) detected; concordance improved to 44/48 (92%) for samples with HIV-2 viral loads >50 RNA copies/mL. The Alere q HIV-1/2 RUO viral load test had a lower limit of detection of HIV-2 RNA in plasma of ~50 copies/ml (input volume=25μL; $HIV\text{-}2_{ROD}$ standards calibrated on the UW m2000 assay) . The Alere test was able to quantify HIV-2 plasma viral load with good linearity for both HIV-2 groups A and B in samples from 50 to 500,000 copies/ml (R^2>0.99).

Conclusions: The Alere q HIV-1/2 Detect test is a novel, rapid and simple device that detects HIV-2 RNA in clinical samples and differentiates between HIV-1 and HIV-2 with a high level of specificity. It is designed to use small samples (finger prick; 25μL) of whole blood and plasma and has the potential for use as a rapid HIV-2 NAT-based diagnostic and a viral load monitoring device in resource-limited settings, as well as providing confirmation of HIV-2 infection in the new CDC algorithm for HIV testing.

615 Performance of HIV Viral Load with Dried Blood Spots in Children on ART in Mozambique

Amina M. de Sousa Muhate[1]; James C. Houston[2]; Mariamo Assane[1]; Joy Chang[2]; Emilia Koumans[2]; Ilesh V. Jani[1]; Jennifer Sabatier[2]; Paula M. Vaz[3]; Chunfu Yang[2]; Emilia Rivadeneira[2]

[1]Ministry of Health, Mozambique, Mozambique; [2]Centers for Disease Control and Prevention, Atlanta, GA, US; [3]Fundação Ariel Glaser Contra o SIDA Pediátrico, Maputo, Mozambique

Background: The World Health Organization (WHO) recommends using HIV viral load (VL) to monitor antiretroviral treatment (ART) and detect virologic failure (VF) (>1000 copies/mL). However, the gold standard sample, plasma, is challenging to process for patients living in remote areas due to requirements for plasma separation, transportation, and storage. Dried blood spots collected by finger stick (FS-DBS) can overcome the stringent requirements of plasma for VL testing and allow more patients to access the HIV VL test. However there is limited evidence on the validity of FS-DBS to estimate VF at 1000 copies/ml and no evaluations have focused on children. In this study, we compared the performance of HIV VL testing using DBS as an alternative to the plasma for VL testing for children on ART.

Methods: Paired plasma and FS-DBS were collected from 717 children on ART 12 months at six sites in Maputo, Mozambique. Plasma was prepared from venous blood. DBS were prepared for each child by lay health care workers who used finger-sticks to collect blood in micro-EDTA tubes and spotted DBS (FS-DBS) with transfer pipette with 75 μL of blood per spot. Plasma VL was performed using COBAS Amplipre/COBAS TaqMan HIV-1 Test, V 2.0 and DBS VL was tested using Abbott m2000 HIV-1 DBS Quant, V4 with one spot per test at CDC-Atlanta. All statistical analysis accounted for clustering within sites.

Results: The performance characteristics of DBS VL at thresholds of 1000, 3000, and 5000 copies/mL were compared with plasma VL at 1000 copies/mL as the gold standard. The sensitivity and specificity for each DBS VL threshold were estimated (Table 1).

Threshold (≥ copies/ml)	Sensitivity (%)	Specificity (%)	Kappa	False negative (%)	False positive (%)
Plasma:DBS	95% CI	95% CI	95% CI		
1000:1000	79.8 (61.2, 90.8)	97.6 (93.8, 99.1)	0.79 (0.72, 0.86)	20.2	2.4
1000:3000	70.6 (51.3, 84.5)	98.8 (94.2, 99.8)	0.72 (0.65, 0.79)	29.4	1.2
1000:5000	63.4 (46.9, 77.2)	99.3 (97.1, 99.8)	0.66 (0.59, 0.73)	36.6	0.7

Table 1. Sensitivity, Specificity, and Kappa agreement by DBS VF threshold compared to gold standard plasma Roche among children (n=717)

Conclusions: Our DBS VL data demonstrated very good specificities (97.6%, 98.8%, 99.3%) or low false positivity rates for VF at all three thresholds meaning that very few patients will be misclassified for treatment failure when using this methodology for collecting and analyzing DBS for VL testing. However the sensitivity was lower at all thresholds (79.8, 70.6, 63.4) thus clinicians must be aware of the possibility of false negative results and need to take into account clinical findings when interpreting FS-DBS VL. The false negativity rate was lowest using the threshold of 1000 copies/ml 20.2% vs 29.4 (3000 copies/ml) or 36.6 (5000 copies/ml). Therefore, 1000 copies/mL can be used as the threshold to monitor ART and detect treatment failure when using DBS for VL testing.

616 Cost-Effectiveness of Pooled PCR Testing of Dried Blood Spots for Infant HIV Diagnosis

Cari van Schalkwyk[2]; Jean Maritz[2]; **Alex Welte**[1]; Gert U. van Zyl[2]; Wolfgang Preiser[2]

[1]University of Stellenbosch, South Africa, Stellenbosch, South Africa; [2]University of Stellenbosch, Tygerberg, South Africa

Background: Early diagnosis and initiation on antiretroviral therapy is important for the improved prognosis of HIV infected infants. In resource limited settings, restricted access to qualitative polymerase chain reaction (PCR) amplifies the need for diagnostic tools with improved cost-effectiveness. This study investigates the potential savings achievable by pooling dried blood spots (DBS) for PCR testing, defined as combining multiple patient samples in a single assay run with subsequent individual testing of positive pools. Pooling has previously been shown to enhance efficiency of virological monitoring of therapy.

Methods: Testing demand and technician and reagent costs at a centralised laboratory in the Western Cape, South Africa were monitored. Preparation time and sensitivity/specificity of both the pooling strategy and individual testing was determined on a sample of 295 specimens in 39 HIV reactive and 20 HIV non-reactive pools, using an automated commercial PCR platform. A dynamic model, using all this data as inputs, was built to simulate cost savings for a one year period.

Results: The laboratory feasibility study confirmed the utility of the pooling approach, achieving a sensitivity of 100% (35/35; or, when low-positive/inconclusive samples were included 38/39 i.e. 97.4%), as well as a specificity of 100% (20/20). From July 2012 to June 2013, this lab received an average of 38 samples per day with an overall HIV prevalence of 2%. Savings would have been 66% of direct laboratory costs if a pooling strategy of 5 DBS per pool was followed. Larger pool sizes are theoretically more cost effective but infeasible within the present automated extraction procedure. Technician time spent would only be marginally less, but the median number of runs per day would have reduced by 50%. Figure 1 illustrates percentage cost saved per year, as a function of prevalence, at different pool sizes, for a laboratory that tests 150 samples per day.

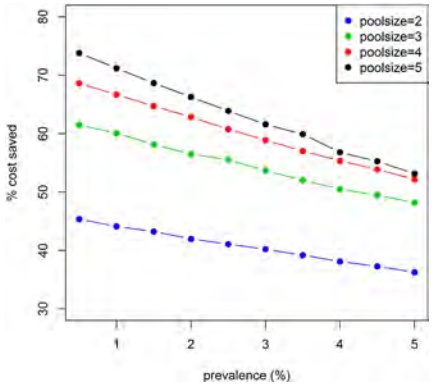


Figure 1: Percentage cost saved per year, as a function of prevalence, at different pool sizes, for a laboratory that tests 150 samples per day.

Conclusions: Pooled PCR testing for infant diagnosis of HIV can significantly reduce diagnostic costs in settings with moderate to low prevalence rates of HIV. Apart from savings on existing programmes, this may reduce barriers to introducing additional testing opportunities, either at additional sites, or at earlier time points, such as delivery for high risk pregnancies.

617 Evaluating Dried Blood Spot Performance in Assessing HIV Treatment Failure in Uganda

Allen Roberts; Herbert C. Duber; Ming Chang; Anne Gasasira; Gloria Ikilezi; Jane Achan; Joan Dragavon; Glenda Daza; Emmanuela Gakidou; Robert W. Coombs

Makerere University College of Health Sciences, Kampala, Uganda

Background: HIV RNA viral load (VL) testing for patients on antiretroviral therapy (ART) has increasingly been recognized as a key component of patient monitoring, even in low-resource settings. However, due to financial and technical constraints, the routine implementation of virologic testing remains rare in most sub-Saharan Africa health facilities. Dried blood spots (DBS) have emerged as a potential low-cost substitute for standard plasma assays; however, their performance in large-scale field conditions has not sufficiently been assessed. In a prospective study in Uganda, we evaluate the ability of a novel whole blood finger-prick DBS assay to detect plasma viral load measures exceeding 1000 and 5000 copies/mL.

Methods: Samples were collected from over 3000 ART patients at nine hospitals and six health centers. 150-250 consecutive adult patients who presented for care and had been on treatment for a minimum of six months were recruited into the study at each facility. Whole blood samples were collected by finger prick onto DBS cards, which were dried, packaged with desiccant, and shipped to the University of Washington for analysis. Two 50-μL DBS were eluted in 1.3-mL lysis solution, extracted by NucliSENS miniMag, and quantified using the Abbott Real Time HIV-1 m2000rt 1.0-mL protocol with a detection level of 520 copies/mL. Paired plasma samples were analyzed with the Roche COBAS AmpliPrep/COBAS TaqMan assay at Joint Clinical Research Centre facilities in Uganda. Correlations, sensitivity, specificity, and positive and negative predictive values were calculated to compare the two methods.

Results: Valid DBS and plasma results were obtained for 2663 patients. The correlation between log-transformed DBS and plasma measures was 0.673. At the 1000 copies/mL threshold, the DBS assay had 73.2% sensitivity, 97.2% specificity, 79.2% positive predictive value (PPV), and 96.1% negative predictive value (NPV). At the 5000 copies/mL threshold, DBS sensitivity was reduced to 49.5% with high specificity (99.5%), PPV (92.6%) and NPV (94.4%).

Conclusions: While the assay sensitivity improved at the lower threshold (1000 copies/mL), under field conditions the method was not sufficiently accurate to substitute for plasma measurement in determining treatment failure. Possible factors associated with low sensitivity include small spot sizes and sample degradation during storage. Further research is needed to improve assay sensitivity and develop scalable sample collection protocols.

618 Comparison of Pooled RNA and 4th Gen Ag/Ab Testing to Identify Acute HIV Infection

Gary Murphy; Simon Carne; Bharati Patel; Elaine Mckinney; Samual Moses; Noel Gill; John Parry; Jennifer Tosswill

Public Health England, London, United Kingdom

Background: To determine in populations at high risk of HIV infection, whether screening of pooled anti-HIV negative specimens for HIV RNA identifies more acute infections than testing specimens by 4th generation assays. To confirm the limitations of 3rd generation screening in high risk populations and discuss its implications for point of care testing.

Methods: Analysis involved 3570 specimens from men who have sex with men (MSM) from two central London STI Clinics and 1837 specimens from heterosexual men of black African ethnicity from a further 2 STI clinics. All specimens had been found to be anti-HIV negative by a 3rd generation anti-HIV assay and were aliquoted to create mini-pools of 8 specimens each. 6 mini-pools went into a Master pools which had maximum of 48 specimens. The master pools were then tested using an in-house real time quantitative taqman probe based assay targeting HIV-1 LTR and *pol*. Reactive pools were broken down to reveal the individual reactive specimen. Any specimens identified as HIV positive by the RNA assay but negative by the third generation ELISA assay were further tested with a 4th generation Ag/Ab assay.

Results: Of the 5407 anti-HIV negative specimens, 6 were found to be HIV RNA positive. In 3rd generation antibody only testing the specimens were clearly negative with a range of activity of 0.041 -0.508 OD/CO. Using the 4th generation HIV antigen/antibody combination assay all six were positive (OD/CO ranges 4.66 – 19.64). All of the six specimens came from men who have sex with men and five of the six came from one centre.

Conclusions: 4th generation screening is the standard of care in the UK and our data does not support the development of a national scheme to screen anti-HIV negative specimens for HIV RNA. The benefits of RNA screening such as potential earlier diagnosis maybe outweighed by the increased turnaround time for pooled RNA testing and the potential loss to follow up by this delay. However, in a high throughput laboratory that screens a high incidence population, a local application of pooled RNA testing may be applicable. The increasing use of home testing and point of care tests that are often only 3rd generation in nature is of more concern as those acutely infected, and therefore at their most infectious, may be missed and our data supports that 4th gen formats for HIV screening programmes will avoid missing diagnosis.

619 Improved Viral Load Monitoring Capacity With Rank-Based Algorithms for Pooled Assays

Tao Liu[1]; **Joseph Hogan**[1]; Renxia Huang[3]; Rami Kantor[2]

[1]Brown University, Providence, RI, US; [2]Miriam Hospital, Alpert Medical School, Brown University, Providence, RI, US; [3]Fulcrum Analytics Inc, Fairfield, CT, US

Background: HIV viral load (VL) monitoring is recommended globally for patients on antiretroviral therapy (ART). However, cost and infrastructure in resource limited settings (RLS) still limit widespread implementation of this guideline.

VL pooling reduces the number of assays needed to ascertain individuals' VL. However, existing pooling methods ignore information from *routinely-collected clinical markers* (RCMs), such as CD4 count and percent. RCMs are correlated with VL and provide valuable information that can be utilized to improve the efficiency of pooling by reducing the number of assays needed for deconvolution.

Methods: We develop a deconvolution algorithm that uses RCMs to determine an optimal individual sample testing sequence for resolving a positive pool (e.g. having a detectable VL). We first use RCMs in a prediction model to estimate risk of viral failure for each sample in a positive pool. Individual samples are then assayed sequentially in a descending order of their risk scores, following a stopping algorithm that dictates whether subsequent assays of remaining samples 'in the pool' are needed. Using simulation models informed by clinical data, we examine the potential advantages of our approach by comparing it to (1) individual VL testing; (2) standard pooling (VL assay of pooled samples followed by VL assays of individual samples for a positive pool); and (3) algorithm-based pooling (VL assay of pooled samples, followed by sequential VL assays of individual samples and a stopping rule that depends on updated VL values for samples remaining in the pool [May et al. JAIDS 2010]). Simulations were based on data from 597 women at the Miriam Hospital HIV Clinic (Providence, USA). Markers used for risk prediction included CD4 count, CD4%, and their 6-month changes. Viral failure was defined using three VL thresholds: 150, 400, and 1000 copies/mL.

Results: The cohort had a median VL 75 copies/mL (IQR 75~400), CD4 count 407 cells/μL (IQR 254-576), and CD4% 23 (IQR 17-30). The Table depicts the expected number of VL assays required for each method and the percent reduction in VL tests compared to individual testing. Standard deconvolution may need more assays depending on the VL threshold. Algorithm-based deconvolution reduces the number of VL tests by 18-35%; our rank-based algorithm further reduces VL assays by 26-45%.

ART Failure Threshold (copies/mL)	ART Failure Prevalence	Expected Number of VL Assays Required to Determine Individual-Level Viral Failure (% of Reduction Compared with Individual Testing)			
		Individual Testing	Standard Deconvolution*	Algorithm-Based Deconvolution*	**Rank-based Deconvolution***
VL > 150	30%	597 (REF)	698 (-17)	489 (18)	**444 (26)**
VL > 400	25%		598 (-0.2)	426 (29)	**373 (38)**
VL > 1000	20%		548 (8.2)	387 (35)	**331 (45)**

* Pooling Size = 5.

Conclusions: Rank-based deconvolution based on RCMs can substantially increase the capacity of comprehensive VL monitoring, suggesting its potential utility in RLS.

WEDNESDAY, FEBRUARY 25, 2015

Session P-M2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Comparison of HIV Incidence Assays

620 Evaluation of Determine™ HIV-1/2 Ag/Ab Combo in the Context of Acute HIV Screening

Silvina Masciotra[1]; S. Michele Owen[1]; Wei Luo[1]; Emily Westheimer[2]; Stephanie Cohen[3]; Laura Hall[4]; Cindy L. Gay[5]; Philip J. Peters[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]New York City Department of Health and Mental Hygiene, New York, NY, US; [3]San Francisco Department of Public Health, San Francisco, CA, US; [4]ICF International, Atlanta, GA, US; [5]University of North Carolina, Chapel Hill, NC, US

Background: Determine™ HIV-1/2 Ag/Ab Combo (DC) is an FDA-approved 4th generation rapid test that can distinguish HIV antigen and antibody reactivity, but performance in the new HIV diagnostic algorithm has not been evaluated. Data on the performance of DC on whole blood from individuals in early phases of infection are limited. We evaluated the performance of DC with plasma and whole blood.

Methods: We tested two sets of samples with DC and compared results to previous data from the APTIMA RNA assay (Aptima), Abbott ARCHITECT (ARC), Multispot HIV-1/HIV-2 rapid test (MS), and OraQuick ADVANCE (OQ). The sets included a subset of 178 plasma samples collected in the STOP study, a multi-site, prospective study evaluating methods to detect acute infection and 54 sequential plasma samples from 12 seroconverters to which washed red blood cells were added to simulate whole blood at 40% hematocrit. The number of DC-reactive samples and days after the first positive Aptima were calculated for samples from seroconverters. Statistical analysis was done using the McNemar's test.

Results: Among the STOP specimens, the 4th generation lab-based ARC detected 19 more infections than DC (*p=0.0001*) (Table). Of 107 ARC-positive samples, DC detected 52.6% of the acute infections (p<0.0001) and 98.6% of the established infections (p=1.00). DC also identified 93.3% of HIV established infections in plasma that were not detected with OQ using whole blood at the screening sites (*p=0.0001*).

Among seroconverters, of 54 Aptima-positive/ARC-positive/MS-neg or –indeterminate samples, DC was reactive in 52 (96.3%) of plasma and 36 (66.6%) of whole blood (*p=0.003*) and OQ was reactive in 14 (26%) in plasma. The reactivity of DC in whole blood was 17 Ag+, 2 Ag+Ab+, and 17 Ab+. Whole blood reactivity was delayed in 7/12 seroconverters compared with plasma. Overall, the median delay in reactivity with whole blood compared to plasma was two days.

Performance of DC in specimens from the STOP study

Results from previous testing	n	Determine Combo reactive results
Acute HIV-1 infections		
Aptima-pos/ARC-neg	10	0 (0%)
Aptima-pos/ARC-pos/MS-neg or -ind/OQ-neg*	38	12 Ag+, 8 Ab+ (52.6%)
Established HIV-1 infections		
ARC-pos/MS-pos/OQ-neg*	15	1 Ag+Ab+, 13 Ab+ (93.3%)
ARC-pos/MS-pos/OQ-pos*	54	1 Ag+Ab+, 53 Ab+ (100%)
False positive 4th generation specimens		
Aptima-neg/ARC-pos/MS-neg or -ind/OQ-neg*	61	3 (5%)

*pos: positive; neg: negative; ind: indeterminate; Ag: antigen; Ab: antibody; *Aptima, ARC and MS were performed in plasma, OQ was performed in whole blood at the screening site*

Conclusions: DC used with plasma detected fewer specimens with acute HIV infection compared to an instrumented lab-based 4th generation as ARC. DC became reactive later with whole blood than with plasma, but earlier than OQ used with plasma, which may be partially due to detection of antigen in whole blood. Thus, if CLIA-waived, DC would likely represent an advantage over other rapid tests in detecting infections earlier in settings where lab-based testing is not feasible.

621 Performance of the Geenius HIV-1/HIV-2 Assay in the CDC HIV Testing Algorithm

Kevin P. Delaney; Steven Ethridge; Laura G. Wesolowski; MIchele Owen; Bernard M. Branson

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: CDC recently released new guidelines for laboratory diagnosis of HIV infection in the United States (the "CDC algorithm"), which recommends use of an assay that differentiates HIV-1 from HIV-2 after a reactive HIV-1/HIV-2 screening test. Currently only the Multispot HIV-1/HIV-2 differentiation test (MS) is FDA-approved for this use. A new test, the Geenius HIV-1/HIV-2 Supplemental assay (Geenius), has been proposed to replace MS.

Methods: We evaluated Geenius with a panel of specimens previously tested with FDA-approved screening tests, MS and the Aptima RNA assay (NAT) and classified by the CDC algorithm. The 873 specimens included 658 classified as HIV-1 by the CDC algorithm (HIV1+), 8 classified as acute HIV-1 infections (acute), and 207 specimens with reactive results on at least one HIV-1/HIV-2 screening test identified from 4500 previously collected specimens classified as negative (HIV-): 176 with a reactive HIV screening test result other than MS, 5 reactive on another screening test and MS, and 26 with only a reactive MS screening test result. We compared Geenius results with those from the CDC algorithm and MS.

Results: Of 658 HIV1+ specimens, Geenius classified 654 (99.4%) as HIV1+, 1 as HIV-, 1 as HIV-1 indeterminate (HIV-1 IND), and 2 as HIV-positive "untypeable." (Both these specimens were initially positive for both HIV-1 and HIV-2 with MS, but classified as HIV-1 after dilution). Thirteen additional HIV1+ specimens that were positive for both HIV-1 and HIV-2 by MS before dilution were positive for HIV-1 only by Geenius. One of 8 acute HIV specimens was HIV-2 IND by Geenius and HIV- by MS; all others were HIV- with both tests. Of the 181 HIV- specimens with a reactive non-MS screening test result, 165 (91.2%) were classified as HIV- by Geenius; one of the remaining 16 was classified as HIV1+. Of 31 HIV- specimens with a reactive MS screening result, 24 were classified as HIV- by Geenius; none were concordantly reactive with MS and HIV-1 positive by Geenius. The majority of the non-negative Geenius results were HIV-2 IND (Table). All HIV- specimens categorized as HIV-2 IND were attributable to reactivity at the gp140 HIV-2 peptide line only.

Comparison of Geenius and Multispot HIV-1/HIV-2 differentiation assay results for 207* specimens classified as HIV-negative by the CDC algorithm for laboratory diagnosis of HIV infection but reactive by one or more HIV screening tests

		Geenius HIV-1/HIV-2 differentiation assay interpretation							Total
		HIV Negative	HIV Indeterminate	HIV-2 Indeterminate	HIV-1 Indeterminate	HIV Positive, "Untypeable"	HIV-2 Positive	HIV-1 Positive	
Multispot supplemental test interpretation**	HIV-1 Only (both spots)								0
	HIV-2 Only								0
	HIV-1/HIV-2 Undifferentiated	1		1					2
	HIV-1 Indeterminate (only 1 of 2 spots)	3							3
	HIV Negative	161		13	1			1	176
Multispot screening test interpretation***	Reactive	24	2	4	1	0	0	0	31

*207 specimens with false-reactive results on one or more HIV screening tests were obtained from a previous study of 4500 HIV-negative specimens.

** Multispot supplemental test interpretation: reactivity at both HIV-1 spots required for positive; reactivity at only one of two HIV-1 spots is considered indeterminate; reactivity at both HIV-1 and HIV-2 spots is considered HIV-1/HIV-2 undifferentiated.

***Multispot screening test interpretation: any reactivity at any spot is considered reactive; the 31 include 5 with reactivity to another HIV-1/HIV-2 screening assay

Conclusions: The ability of the Geenius to detect established and early HIV infection is similar to the MS currently used in the CDC algorithm, but more IND results, particularly HIV-2 IND results, occur with Geenius.

622 The Effect of HIV-1 Subtype A, C and D on Cross-Sectional Incidence Assay Performance

Andrew F. Longosz[2]; Mary Grabowski[2]; Charles S. Morrison[3]; Ronald H. Gray[2]; Connie Celum[4]; Quarraisha Abdool Karim[5]; Hilmarie Brand[6]; Thomas C. Quinn[1]; Susan H. Eshleman[2]; **Oliver B. Laeyendecker**[1]
[1]National Institute of Allergy and Infectious Diseases, Baltimore, MD, US; [2]Johns Hopkins University, Baltimore, MD, US; [3]FHI 360, Durham, NC, US; [4]University of Washington, Seattle, WA, US; [5]CAPRISA, University of KwaZulu-Natal, Congella, South Africa; [6]SACEMA, Stellenbosch University, Stellenbosch, South Africa

Background: We examined the impact of HIV subtype A, C and D on the performance of serologic cross-sectional HIV incidence assays.

Methods: Three assays were evaluated: the limiting antigen avidity enzyme immunoassay (LAg-Avidity assay), the BED capture enzyme immunoassay (BED-CEIA), and an avidity assay based on the Genetic Systems 1/2 + O ELISA (BioRad-Avidity assay). We evaluated 4,821 plasma and serum samples from individuals known to be infected with HIV-1 subtypes A, C and D from 6 different cohort studies in Zimbabwe, Uganda, South Africa, Kenya, Zambia and Botswana. This study included 2,045 subtype A samples (212 samples from the 2008-2009 Rakai Community Cohort Study (RCCS) and 1,833 samples from the Ugandan Genital Shedding (GS) Study. 1,697 subtype C samples (329 samples from the Ugandan and Zimbabwean GS Studies, 85 samples from HPTN 039, 727 samples from the Partners in Prevention Study and 556 samples from the CAPRISA 004 Trial Group) were analyzed. 1,079 subtype D samples (781 samples from the Ugandan Genital Shedding (GS) Study and 298 samples from the 2008-2009 RCCS) were tested. Date of HIV seroconversion was defined as either the midpoint between the last negative and first positive HIV antibody test, or fifteen days after acute infection was documented (defined as HIV RNA positive / HIV antibody negative). Viral load and HIV-1 subtype data were determined previously in parent studies. Mean duration of recent infection (MDRI) was calculated for subtypes A, C and D using a time window of two years post-seroconversion. To define recent infection, assay cutoffs of 1.5 normalized optical density (OD-n), 0.8 OD-n and 40% avidity index (AI), were used for the LAg-Avidity assay, BED-CEIA, and Bio-Rad-Avidity assay respectively. The false recent rate (FRR), the fraction of samples misclassified as recent, was calculated for all samples and those with detectable viral loads (>400 cps/ml).

Results: There were significant differences for MDRI and FRR estimates by subtype for all three assays (see Table). The largest differences in MDRI were seen for the LAg-Avidity and BED-CEIA assays between subtypes A and D. FRR results were significantly higher for subtype D for all three assays.

Table. Estimated test properties (95% confidence intervals) for each assay, by subtype

Recent/nonrecent threshold (unit)	Number of subjects (data points)	LAg-avidity 1.5 OD-n	BED 0.8 OD-n	BioRad avidity 40% AI
MDRI (days)[a]				
Subtype A	82 (577)	160.5 (144.6-175.7)	291.5 (278.0-303.6)	121.7 (111.7-132.8)
Subtype C	490 (1115)	127.9 (117.0-137.9)	204.9 (194.5-215.3)	138.0 (128.7-147.5)
Subtype D	30 (223)	204.6 (178.2-228.9)	281.0 (258.2-301.1)	150.6 (120.8-180.5)
FRR (%)				
Subtype A	290 (1468)	1.36 (0.83-2.09)	15.0 (13.2-17.0)	0.27 (0.07-0.70)
Subtype C	491 (582)	2.58 (1.44-4.22)	7.39 (5.40-9.82)	0.86 (0.28-1.99)
Subtype D	329 (856)	12.4 (10.3-14.8)	19.9 (17.2-22.7)	13.7 (11.4-16.2)
FRR (%) for VL+				
Subtype A	290 (1352)	0.52 (0.21-1.06)	13.3 (11.5-15.2)	0.30 (0.08-0.76)
Subtype C	451 (547)	2.38 (1.27-4.03)	6.95 (4.96-9.41)	0.73 (0.20-1.86)
Subtype D	328 (705)	6.24 (4.57-8.29)	13.6 (11.2-16.4)	13.8 (11.3-16.5)

AI, avidity; FRR false recent rate; LAg, limiting antigen avidity; MDRI mean duration of recent infection; OD-n, normalized optical density; VL+, viral load > 400 cps/ml;
[a] using a T = 2 years

Conclusions: The performance of each of the three assays varied by HIV subtype and subtype D had the highest false recent rates. These results highlight the need to optimize and validate testing algorithms for cross-sectional HIV incidence estimation in populations with the relevant HIV subtype distributions

623 Avidity Assay for Cross-Sectional Incidence Based on a 4th-Generation Combo Ag/Ab EIA

Allison R. Kirkpatrick[1]; Eshan U. Patel[1]; Connie L. Celum[2]; Richard D. Moore[3]; Joel N. Blankson[3]; Shruti H. Mehta[4]; Gregory D. Kirk[4]; Thomas C. Quinn[1]; Susan H. Eshleman[2]; Oliver B. Laeyendecker[1]

[1]National Institutes of Health, Baltimore, MD, US; [2]University of Washington, Seattle, WA, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: Accurate methods for cross-sectional incidence estimation are needed for HIV surveillance and HIV prevention research. Third generation HIV screening tests, such as Genetic Systems (GS) HIV 1 /2 +O ELISA, have been modified for use as incidence assays, but are not available in many countries and may be replaced with more sensitive 4th generation HIV assays. We developed an HIV avidity assay based on the 4th generation GS HIV Combo Ag/Ab EIA (BioRad Combo assay) and evaluated its performance.

Methods: The BioRad Combo assay was modified by diluting samples 1:10 and incubating them for 30 minutes at 4°C, with and without 0.025 M diethylamine (DEA). The avidity index (AI) was calculated as the optical density ratio of the DEA-treated to the untreated well. We analyzed 1,541 samples from the United States that were collected in the HIV Network for Prevention Trials (HIVNET) 001/001.1 study, the AIDS Linked to the Intravenous Experience Study (ALIVE) cohort, the Johns Hopkins Hospital Clinical Cohort (JHHCC), and the Johns Hopkins Elite Suppressor cohort (ES). Assay performance was assessed using the modified BioRad Combo assay alone, or with a viral load (VL) assay (classifying samples with a VL <400 copies/mL as non-recent). HIVNET 001 samples were used to estimate the mean duration of recent infection (MDRI) using a time window of 2 years for AI cut-offs of 20-90%. The false recent rate (FRR, fraction of samples misclassified as recent), was calculated for the ALIVE and JHHCC samples. Assay reproducibility was also evaluated.

Results: Table 1 shows the performance characteristics of the modified BioRad Combo assay at different AI cutoffs alone and in combination with VL. Neither of these approaches provided a MDRI >100 days with a FRR <1%. All samples from elite suppressors had an AI >80%. AI values were significantly correlated between two technologists (r=0.93; p<0.01).

Table 1. Performance of the BioRad Combo avidity assay in subtype B populations.

Avidity Index	BioRad Combo Avidity		BioRad Combo Avidity + HIV VL>400 c/mL	
	MDRI (95% CI)	FRR % (95% CI)	MDRI (95% CI)	FRR % (95% CI)
Cohort	HIVNET 001 n=801	ALIVE + JHHCC n=702	HIVNET 001 n=801	ALIVE + JHHCC n=702
20%	69 (46, 87)	0.1 (0.0, 0.8)	65 (35, 82)	0.0 (0.0, 0.5)
30%	86 (63, 102)	0.7 (0.2, 1.7)	79 (57, 94)	0.4 (0.1, 1.2)
40%	105 (87, 120)	1.6 (0.8, 2.8)	95 (75, 108)	0.9 (0.3, 1.9)
50%	123 (105, 136)	2.1 (1.2, 3.5)	109 (91, 122)	1.1 (0.5, 2.2)
60%	137 (122, 150)	3.4 (2.2, 5.0)	119 (103, 131)	2.1 (1.2, 3.5)
70%	159 (146, 171)	5.1 (3.6, 7.0)	136 (123, 147)	3.1 (2.0, 4.7)
80%	178 (165, 190)	6.3 (4.6, 8.3)	152 (140, 162)	3.4 (2.2, 5.0)
90%	221 (208, 235)	9.1 (7.1, 11.5)	186 (170, 199)	4.6 (3.1, 6.4)

Conclusions: The performance characteristics of this assay suggest that it may be useful as one component of a multi-assay algorithm (MAA) for HIV incidence estimation. When combined with a VL exclusion the FRR was halved but MDRI estimates were reduced by approximately 10%. This may provide a useful tool for HIV incidence estimation in the future, if 3rd generation HIV screening tests are replaced with 4th generation tests for HIV diagnosis. Further research is needed to evaluate the modified BioRad Combo assay in combination with other assays to accurately estimate HIV incidence based on 4th generation HIV tests.

624 Estimation of HIV Incidence in a High-HIV-Prevalence Setting, South Nyanza, Kenya, 2012

Andrea A. Kim[1]; David Maman[2]; Harrison Fredrick Omondi[3]; Alex Morwabe[3]; Irene Mukui[4]; Valarie Opollo[3]; Beatrice Kirubi[5]; Jean-François Etard[2]; Martinus W. Borgdorff[7]; **Clement Zeh**[7]

[1]US Centers for Disease Control and Prevention, Dpo, AE, US; [2]Médecins Sans Frontières, Paris, France; [3]Kenya Medical Research Institute (KEMRI)/CDC Research and Public Health Collaboration, Kisumu, Kenya; [4]Kenya Ministry of Health, Nairobi, Kenya; [5]Médecins Sans Frontières, Nairobi, Kenya; [6]US Centers for Disease Control and Prevention (CDC), Kisumu, Kenya; [7]US Centers for Disease Control and Prevention (CDC), Kisumu, Kenya

Background: Tests for recent infection (TRI) use immunological markers to distinguish recent from chronic HIV infection, providing the ability to estimate HIV incidence and evaluate HIV prevention interventions. Several candidate TRIs, including the Limiting Antigen Avidity Enzyme Immunoassay (LAg) and Bio-Rad Avidity Enzyme Immunoassay (Bio-Rad) are being validated for field performance. We evaluated the performance of the LAg and Bio-Rad in Ndiwha District in South Nyanza, Kenya, a setting with a HIV prevalence of 24% and availability of high-impact HIV prevention interventions.

Methods: In 2012, we conducted a two-stage cluster sample household survey of persons aged 15-59 years residing in Ndhiwa District to estimate HIV incidence. Participants testing HIV+ using the national rapid HIV testing algorithm provided a blood sample to test for viral load and recent infection. A person was determined to have recent infection if they 1) tested recent on the TRI; 2) were not virally suppressed, i.e., had an HIV-1 RNA concentration ≥ 400 copies/mL; and, 3) were HIV treatment naive. Cross-sectional incidence was calculated using a mean duration of recent infection of 130 days [95% confidence interval (CI) 118-142] for LAg and 239 days (CI 214-265) for Bio-Rad, and a false-recent rate (FRR) of 0.5% (CI 0.01-0.95) for LAg and 2.4% (CI 1.4-3.4) for Bio-Rad. An incidence to prevalence (I:P) ratio was calculated to assess plausibility of the incidence estimate.

Results: Among 6,095 participants, 1,465 were HIV+; 29 tested recent with LAg and 68 with Bio-Rad. HIV incidence was 1.5% (CI 0.6–2.3) with LAg and 1.3% (CI 0.5–2.1) with Bio-Rad. HIV incidence among women was two times higher than among men, respectively, with LAg (2.0%, CI 0.9–3.2 vs. 0.7%, CI 0–1.5) and Bio-Rad (1.6%, CI 0.6-2.0 vs. 0.8%, CI 0–1.7). HIV incidence peaked among persons aged 25-34 years with LAg (1.6%, CI 0.5–2.7) and persons aged 35-45 years (2.2%, CI 0.4–3.7) with Bio-Rad. Among persons aged 45+ years, HIV incidence was negative with Bio-Rad (-0.3%, CI -1.4-0.7) and 0.3% (CI 0-1.4) with LAg. The I:P ratio increased monotonically with age with LAg but not with Bio-Rad.

Conclusions: The LAg and Bio-Rad produced similar HIV incidence estimates overall and by sex. Age-specific trends in incidence and prevalence were epidemiologically plausible with LAg but not with Bio-Rad. Negative incidence with Bio-Rad suggests that the sample size was either too low or FRR too high for generating reliable age-specific incidence estimates with Bio-Rad.

625 False Recent Rates for Two Recent Infection Testing Algorithms, South Nyanza, Kenya

Clement Zeh[1]; David Maman[4]; Harrison Omondi[2]; Alex Morwabe[2]; Collins Odhiambo[2]; Beatrice Kirubi[4]; Irene Mukui[3]; Martinus W. Borgdorff[1]; Jean-François Etard[4]; Andrea A. Kim[1]

[1]US Centers for Disease Control and Prevention, Kisumu, Kenya; [2]Kenya Medical Research Institute, Kisumu, Kenya; [3]National AIDS and STI Control and Prevention, Nairobi, Kenya; [4]Médecins Sans Frontières, Paris, France

Background: Evaluation of candidate tests for recent HIV infection (TRI), designed to distinguish recent from chronic HIV infection, is an essential step prior to estimating cross-sectional HIV incidence. The TRI's false-recent rate (FRR), the probability that a chronic infection will misclassify as recent, is a required parameter for calculating HIV incidence and should not exceed 2% for accuracy. Because the FRR varies by TRI and sub-population, the FRR should be assessed in all settings in which HIV incidence will be estimated. We compare the FRR for the Limiting Antigen Avidity Enzyme Immunoassay (LAg) and Bio-Rad Avidity Enzyme Immunoassay (Bio-Rad), respectively, in a high HIV prevalence setting in South Nyanza, Kenya.

Methods: We conducted a population-based household survey of persons aged 15-59 years in Ndhiwa District in South Nyanza, Kenya. HIV treatment naive participants with documented chronic HIV infection (defined as testing HIV+ in the survey and reporting the first HIV+ test result ≥12 months preceding the survey) were tested for recent infection using the LAg and Bio-Rad on serologic blood samples. Recent infection was defined based on two recent infection testing algorithms (RITA): 1) a multi-assay algorithm (MAA) which defined a recent case as: a) tested recent on the TRI; b) not virally suppressed defined as HIV-1 RNA concentration ≥400 copies/mL; and 2) a single-assay algorithm (SAA) which defined a recent case as tested recent on the TRI. The FRR was calculated by dividing the number of recent cases observed on the RITA by the number of chronic infections tested.

Results: Of 1,465 HIV-positive samples, 835 (57.0%) were chronic infections. Based on the MAA, the FRR was 0.5% (95% CI 0.01 – 1.0) for LAg and 2.4% (95% CI 1.4 – 3.4) for Bio-Rad. Based on the SAA, the FRR was 4.6% (95% CI 3.2 – 6.0) for LAg and 7.2% (95% CI 5.5 – 9.0) for Biorad. The FRR did not differ by sex and RITA, but varied by age group for the two RITAs. In the MAA, the FRR was highest among youth aged 15-24 years (1.2%; 95% CI 0 – 3.5 for LAg; 3.5%; 95% CI 0 – 7.4 for Bio-Rad). In the SAA, the FRR was highest among persons aged 45-59 years at 5.7%; 95% CI 2.8 – 8.6 for LAg and 8.9%; 95% CI 5.4 – 12.5 for Bio-Rad.

Conclusions: The recommended threshold for a FRR was met by LAg, but only in the MAA which excluded individuals with suppressed viral load. Performance of the TRIs using the SAA resulted in high FRRs that are inappropriate for estimating incidence.

626 Viral Load is Critical in Limiting False-Recent Results From HIV Incidence Assays

Reshma Kassanjee[1]; Shelley Facente[2]; Sheila Keating[3]; Elaine McKinney[4]; Kara Marson[2]; Christopher D. Pilcher[2]; Michael Busch[3]; Gary Murphy[4]; **Alex Welte**[1]
The Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA)

[1]South African DST/NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), University of Stellenbosch, Stellenbosch, South Africa; [2]University of California San Francisco, San Francisco, CA, US; [3]Blood Systems Research Institute, San Francisco, CA, US; [4]Public Health England, London, United Kingdom

Background: The cross-sectional use of (biomarker) tests for recent HIV infection in principle offers affordable, low-bias options for incidence estimation. For currently available assays, viral suppression (due to elite control or antiretroviral treatment) is predictive of long-term infections being ('falsely') classified as 'recent'. Surveillance requires a not-too-transient 'mean duration of recent infection' (MDRI) – preferably at least 6 months. Assay readings below a chosen threshold are interpreted as indicating 'recent' infection, and any assay threshold sufficiently high to achieve a large MDRI inevitably incurs a substantial 'false-recent rate' (FRR), which should preferably be no higher than 1%. The performances of seven assays (BED, Limiting Antigen (LAg), Less-Sensitive (LS) Vitros, Vitros Avidity, BioRad Avidity, Architect Avidity, Geenius) were compared, in stand-alone form and in conjunction with a rule that low viral load is indicative of non-recent infection, allowing for varying assay and viral load thresholds.

Methods: Specimens were used from a growing repository, previously described, of over 6000 specimens representing over 2000 subjects from studies in Africa, Brazil and the United States. Assay thresholds were adapted to produce the same MDRI, estimated by binomial regression. Within a model scenario inspired by the contemporary South African context, the net model population-level FRRs were estimated by combining FRR estimates for key subgroups (stratifying by time since infection and treatment status).

Results: Table 1 shows the model population-level FRR for each assay, using an assay threshold that provides an MDRI of 200 days in each case, used either alone or with a viral load rule (using viral load thresholds of 75 and 1000 copies/ml).

	False-recent rate[1]								
Long-infected population	Treatment-naïve[2]			Treated and virally-suppressed			Treatment coverage of 30%		
Viral load threshold (copies/ml)	0	75	1000	0	75	1000	0	75	1000
Architect Avidity	3.9%	4.3%	4.7%	43.1%	0.0%	0.0%	15.7%	3.0%	3.3%
BED	2.1%	2.2%	2.7%	60.4%	0.0%	0.0%	19.6%	1.5%	1.9%
BioRad Avidity	0.8%	0.9%	1.0%	20.9%	0.0%	0.0%	6.8%	0.6%	0.7%
Geenius	3.9%	4.1%	4.4%	68.7%	0.0%	0.0%	23.4%	2.9%	3.1%
LAg	0.6%	0.5%	1.1%	60.5%	0.0%	0.0%	18.5%	0.4%	0.8%
LS-Vitros	4.3%	3.9%	3.3%	67.2%	0.0%	0.0%	23.1%	2.7%	2.3%
Vitros Avidity	3.3%	3.4%	3.3%	61.6%	0.0%	0.0%	20.8%	2.4%	2.3%

[1] For a choice of assay threshold that produces an MDRI estimate of 200 days; MDRI estimated using binomial regression (logit link with a cubic polynomial of time since infection as the predictor)

[2] Survival of treatment-naïve population follows a Weibull distribution with a mean of 10 years and standard deviation of 2.5 years; probability of 'recent' result analysed using binomial regression (described above)

Table 1: False-recent rates for recent infection testing algorithms

Conclusions: Adapted to provide a standard desirable MDRI of 200 days, none of the assays, used alone, provide an acceptably low FRR. With the use of any realistic viral load threshold, the FRR values drop dramatically, to between 0.4% and 3.3%, which is operationally feasible for population-level surveillance in high incidence contexts. Increasing the viral load threshold above 75 copies/ml offered little improvement in FRRs while decreasing MDRIs. Methods for optimally combining all information about predictors of 'false-recent' results into real-world context-specific FRR estimates require further development. Also, judicious combinations of these assays could potentially yield further improvements in performance.

627 Use of the Sample-to-Cutoff Ratio (S/CO) to Identify Recency of HIV-1 Infection

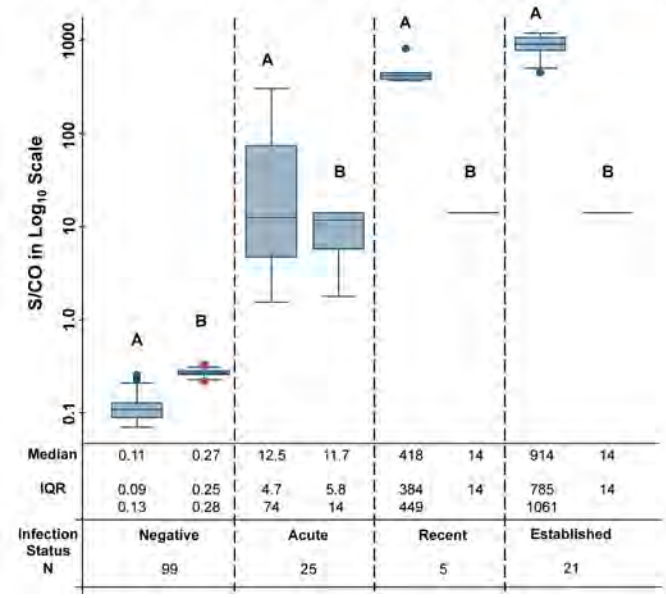
Eric M. Ramos; José Ortega; Glenda Daza; Yuree Namkung; Socorro Harb; Joan Dragavon; Robert W. Coombs
University of Washington, Seattle, WA, US

Background: There are two FDA-approved 4th generation assays available that have the capability to detect both HIV-1/2 specific antibodies and HIV-1 p24 antigen, allowing for the diagnosis of acute HIV-1 infection (AHI). Both assay are considered reactive at sample/cutoff ratio (S/CO)≥1 and non-reactive at S/CO<1. Since the S/CO signal increases with the quantity of antigen and antibodies presents in the sample, it should be possible to use the S/CO range to differentiate between negative, AHI, recent and established HIV infection status.

Methods: All the samples were run with the Abbott ARCHITECT HIV Ag/Ab Combo CMIA (ARCHITECT) and the Bio-Rad GS HIV Combo Ag/Ab EIA (GSCOMBO). The following testing algorithm was used: S/CO<1 with negative nucleic acid amplification test (NAT): negative; S/CO≥1 with Bio-Rad Multispot HIV-1/2 rapid test (MS) non-reactive and positive NAT: AHI; ARCHITECT or GSCOMBO reactive, MS-reactive with a confirming Western blot (WB) without or with the band p31+ present: recent or established infection, respectively.

Results: A total of 150 clinical specimens were evaluated. Ninety-nine samples with a S/CO<1 were confirmed as negative with an ARCHITECT and GSCOMBO S/CO median and interquartile range [IQR] of 0.11 [0.09-0.13] and 0.27 [0.25-0.28], respectively. Fifty-one samples had a S/CO≥1, of which 25 confirmed as AHI (Fiebig II) with ARCHITECT and GSCOMBO S/CO median [IQR] of 12.5 [4.7-74] and 11.7 [5.8-14], respectively, and with a viral load median [IQR] of 1.07x10^6 RNA copies/mL [6.90x10^5 - 10x10^6]. Of the 26 specimens that were MS reactive and WB positive, 21 specimens were confirmed as established infection (Fiebig VI) and only 5 lacked the WB-p31+ band, which indicated recent infection (Fiebig V). The ARCHITECT S/CO medians [IQR] for recent and established infection were 418 [384-449] and 914 [785-1061] respectively; both S/CO ratios were the same (14 [14]) for the GSCOMBO. The GSCOMBO S/CO also reached 14 in 40% of AHI (10 samples). There were statistically significant differences in the ARCHITECT S/CO median [IQR] between AHI, recent and long-term infection (Kruskal–Wallis, p<0.0001) but not for GSCOMBO (Figure 1).

Figure 1: Distribution of (A) ARCHITECT and (B) GSCOMBO S/CO values through different HIV stages. N and IQR represent samples number and interquartile range, respectively.



Conclusions: In this small study both the GSCOMBO and ARCHITECT identified AHI equally well but the ARCHITECT S/CO dynamic range was able to further differentiate between AHI, recent and established infection. The use of the ARCHITECT S/CO to identify recency of HIV-1 infection requires confirmation in a larger study.

628 An Abbott Architect Combo Signal to Cut-Off Ratio With Adequate PPV to Confirm HIV

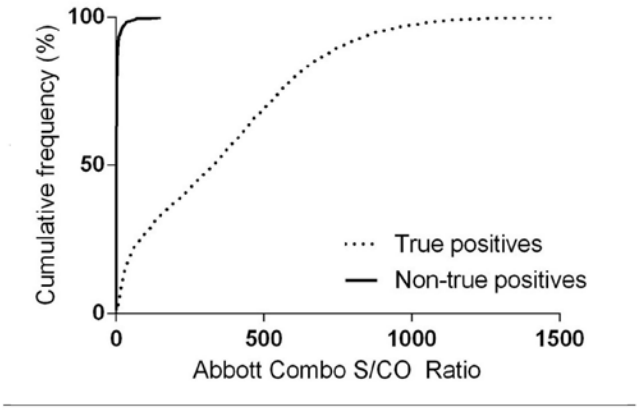
Tomas O. Jensen[1]; Peter Robertson[2]; **Jeffrey J. Post**[1]
[1]*Prince of Wales Hospital, Randwick, Australia;* [2]*South Eastern Area Laboratory Services, Prince of Wales Hospital, Sydney, Australia*

Background: Recent revisions of HIV testing algorithms have aimed to minimise the time to confirmation of the diagnosis without losing sensitivity and specificity which has clear advantages to both patients and clinicians. We hypothesised that the positive predictive value (PPV) of the Abbott Architect HIV Ag/Ab Combo Assay increases with the signal to cut-off (S/CO) ratio and that a S/CO ratio could be identified with a sufficiently high PPV to give a positive result to patients without waiting for the results of supplementary testing.

Methods: All testing episodes were extracted from the laboratory database between March 2006 and March 2014. Samples came from a wide range of adult clinical services including medical and surgical inpatient departments, other laboratories, sexual health clinics, infectious diseases clinics, a women's hospital, IVF clinics, general practitioners and prison health services. Positive tests were classified as true positive or non-true positive depending on synchronous and subsequent supplementary testing with a Western Blot (WB), a HIV p24 Ag assay (confirmed by neutralization), a HIV Ab assay (tested with an alternate EIA) and/or HIV viral load. The data were randomly allocated to two equally sized samples – a train sample and a test sample.

Results: Of 138,911 testing episodes, 3,705 had a positive result. The true positive group included samples with : 1) a synchronous positive WB (N=1,989), 2) an initial negative or indeterminate WB followed by a positive WB within 6 months (N=79), 3) a negative or indeterminate WB and at least two positive results of the p24 Ag assay, the HIV Ab assay or the HIV viral load (N=435), 4) a negative or indeterminate WB and a positive p24 Ag assay without a HIV viral load result available (N=38).The highest non-true S/CO ratio in the train sample was 151.17 and when this was applied to the test sample it had a PPV of 100% and a sensitivity of 67.4%. S/CO ratios of 100 and 50 had a PPV and sensitivity of 99.7% and 73.8% and 99.0% and 80.6% respectively. The frequency distribution of the S/CO ratios of true and non-true positives in the total sample is shown in figure 1.

Figure 1. The cumulative frequency distribution of the S/CO ratios of true and non-true positive Abbott Combo testing episodes.



Abbreviations: S/CO = Signal to Cut-off.

Conclusions: We have shown that knowledge of the S/CO ratio allows for the test result of the Abbott Combo to be used immediately in clinical decision making. Given a sufficiently high S/CO ratio, the clinician will be able to deliver a test result to the patient without waiting for further confirmatory testing with a high degree of clinical certainty.

629 Determining HIV Status of African Adults With Discordant HIV Rapid Tests

Jessica M. Fogel[1]; Estelle Piwowar-Manning[1]; Mark A. Marzinke[1]; William Clarke[1]; Michal Kulich[2]; Jessie K. Mbwambo[3]; Linda Richter[4]; Glenda Gray[5]; Thomas J. Coates[6]; Susan H. Eshleman[1]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Charles University, Prague, Czech Republic; [3]Muhimbili University Teaching Hospital, Dar es Salaam, United Republic of Tanzania; [4]Universities of the Witwatersrand and KwaZulu-Natal, Durban, South Africa; [5]South African Medical Research Council, Cape Town, South Africa; [6]David Geffen School of Medicine and University of California Los Angeles Health, Los Angeles, CA, US

Background: In resource-limited settings, the World Health Organization recommends using two HIV rapid tests for HIV diagnosis. If the test results are discordant, a third tie-breaker test is often used to determine HIV status. We evaluated the HIV status of adults with discordant rapid tests and evaluated the performance of different tie-breaker tests. Samples were obtained from a population-based survey (NIHM Project Accept [HPTN 043]). The frequency of discordant rapid tests in the survey was 2.1% in Tanzania and 0.3% in South Africa.

Methods: Plasma samples (N=173) were classified as HIV positive or HIV negative using a rigorous testing algorithm adapted from the HIV testing algorithm currently recommended by the United States Centers for Disease Control and Prevention. The testing algorithm included two fourth-generation immunoassays (BioRad Combo assay and Abbott Combo assay), an HIV-1/HIV-2 differentiation assay, and two HIV RNA tests. Selected samples were further characterized using a panel of laboratory assays that included a qualitative assay for antiretroviral (ARV) drug detection. Sensitivity, specificity and accuracy were determined for the following tie-breaker tests: a third-generation HIV rapid test, a third-generation enzyme immunoassay (EIA), the BioRad Combo assay, and the Abbott Combo assay.

Results: Twenty-nine (16.8%) of the 173 samples were classified as HIV positive. One sample was from an acute infection. Three (10.7%) of the remaining 28 HIV positive samples had detectable HIV RNA. ARV drugs were detected in only one sample (viral load: 1,280 copies/ml). Sensitivity of the tie-breaker tests was: HIV rapid test: 8.3%; third-generation EIA: 24.1%; BioRad Combo assay: 93.1%; Abbott Combo assay: 96.6%. Specificity of the tie-breaker tests was: HIV rapid test: 96.1%; third-generation EIA: 98.6%; BioRad Combo assay: 88.2%; Abbott Combo assay: 90.3%. Accuracy of the tests ranged from 79.5-91.3%.

Conclusions: Significant differences were observed in the performance of tie-breaker tests for determining HIV status in individuals with discordant HIV rapid test results. Most HIV infections were missed using an HIV rapid test or third-generation EIA as a tie-breaker. In this cohort, most HIV-infected individuals with discordant HIV rapid test results were virally suppressed in the absence of ARV drugs. More rigorous testing approaches, rather than a single tie-breaker assay, may be needed to resolve the HIV status in individuals with discordant rapid test results.

WEDNESDAY, FEBRUARY 25, 2015

Session P-M3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HIV Detection, Tropism, and CD4 Measurement

630 Accuracy of POC CD4 testing using microtube capillary sampling in Botswana households

Sikhulile Moyo[1]; Lillian Okui[1]; Hermann Bussmann[1]; Simani Gaseitsiwe[1]; Erik van Widenfeldt[1]; Molly P. Holme[2]; Joseph Makhema[1]; Shahin Lockman[2]; Vladimir Novitsky[2]; Max Essex[2]

[1]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana; [2]Harvard School of Public Health, Boston, MA, US

Background: Point of care (POC) CD4 cell count can reduce the time to eligibility assessment for antiretroviral treatment and improve linkage to care. In a village household setting in Botswana, we evaluated the performance of field POC CD4 testing versus conventional laboratory-based flow cytometry.

Methods: Capillary blood was collected by finger-prick into EDTA microtubes. Venous blood was collected by venipuncture. Both blood collection procedures were performed in households during annual surveys in the village of Mochudi, Botswana. The Alere PIMA® system was used for POC CD4 testing while laboratory testing was performed using BD FacsCalibur. The Bland-Altman method was used to estimate the mean bias and 95% confidence limits of agreement (LOA). Sensitivity and specificity were calculated for a threshold of 500 cells/uL CD4 cell count.

Results: A total of 155 adults were enrolled with CD4 results for both field POC and lab-based testing. The median age was 32 years old and 63% were females. The median CD4 was 827 (IQR 668, 1058) cells/uL. We observed a mean bias between CD4 measurements by POC and FacsCalibur of -14.1 cells/uL [(95% LOA -327.4 – 299.2), paired t-test p = 0.2740] (Figure 1). Using a threshold of 500 CD4 cells/uL, POC CD4 testing using EDTA capillary sampling into microtube had a sensitivity of 73.3 (95% CI 44.9 – 92.3) cells/uL and specificity of 93.6 (88.1 – 97.0) cells/uL.

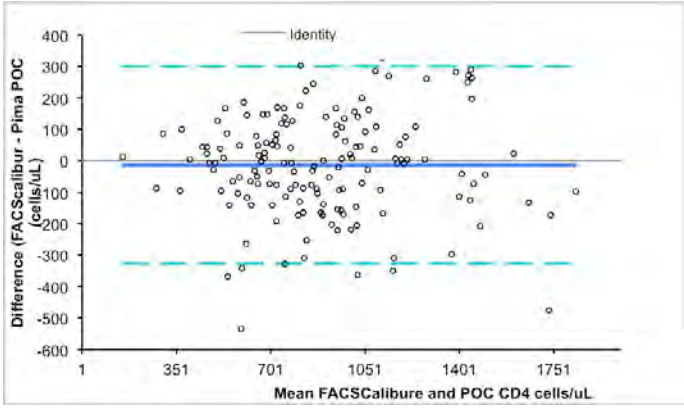


Figure 1: Bland-Altman plot for comparison of Alere PIMA® CD4 using microtube and FACScalibur

Conclusions: The Alere PIMA® POC CD4 testing with EDTA capillary sampling into microtube had one of the lowest non-significant negative mean bias relative to FACScalibur CD4 testing, compared previous findings using finger prick sampling alone. There were few measurements below CD4 threshold of 350 cells/uL and sensitivity was low at threshold of 500 cells/uL, but with good specificity. Coupling HIV testing with POC CD4 in a household setting has potential to close gaps in linkage to HIV care in communities.

631 Zyomyx MyT4 and BD FACSPresto Comparison to the Pima CD4 Assay

Katie Tucker; Sehin Birhanu; Larry Westerman
US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: In conjunction with HIV antiretroviral treatment (ART) scale up, CD4 Point-of-Care (POC) assays are being utilized in resource-limiting settings to provide effective access to CD4 testing and determine eligibility for ART. Since 2009, the Alere Pima CD4 assay has been used for POC CD4 counts in resource-limiting setting and having an impact on HIV patient care. Many new POC CD4 assays are being introduced into the market, including the Zyomyx MyT4 and BD FACSPresto Near-Patient CD4 Counter. We assessed the quality, functionality, and performance of the MyT4 and FACSPresto assays in comparison with the established Pima CD4 assay.

Methods: In 2014, we evaluated the MyT4 and FACSPresto assays. Whole blood specimens were analyzed for CD4 counts with the Pima CD4 and with the MyT4 (n=141) or FACSPresto (n=101). Scattered-plot and Bland-Altman analysis were done with Pima CD4 as the reference method. Precision of each assay was estimated by analyzing 3 specimens ten times on each platform and calculating the coefficient of variation (CV%). Error rates for each CD4 assay were assessed.

Results: Scattered-plots and Bland-Altman analysis indicated that CD4 counts from both the MyT4 (R^2=0.91, y=1.08x-28, bias +2 (-159, +156)) and FACSPresto (R^2=0.96, y=1.15x+11, bias +78 (-59, +214)) correlated with the Pima CD4. CD4 counts with the MyT4 were estimated to have slightly more random error associated with the assay, while the FACSPresto CD4 counts were estimated to have a positive bias. Precision studies estimated the MyT4 to have a slightly higher CV% (8.2%) in comparison to FACSPresto (5.4%) and Pima (5.9%). Error rates increased on both MyT4 and FACSPresto with aged specimens (>12h, >20h), while the Pima CD4 was able to consistently analyze specimens up to 48 hours old.

Conclusions: The Zyomyx MyT4 and BD FACSPresto correlated well with the Alere Pima CD4 and both prove to be acceptable methods for CD4 analysis. Both assays could potentially be used in point-of-care and resource-limiting settings.

632LB Point-of-Care CD4 (Pima) Impact on Linkage to Care With Home-Based HIV Testing, Kenya

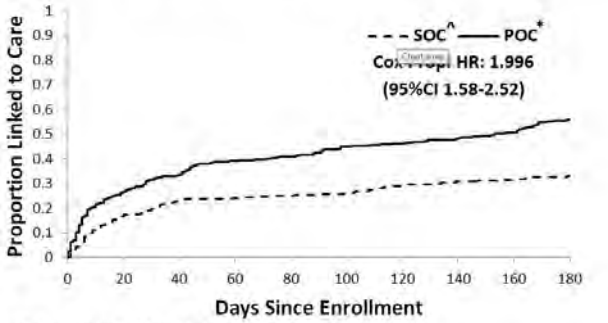
Mitesh A. Desai[1]; Duncan Okal[2]; Robert T. Chen[1]; Richard Ndivo[2]; Charles Lebaron[1]; Tiffany Williams[1]; Fred Otieno[2]; Charles Rose[1]; Taraz Samandari[1]; Clement Zeh[1]
[1]US Centers for Disease Control and Prevention, Atlanta, GA, US; [2]Kenya Medical Research Institute, Kisumu, Kenya

Background: Referral lab-based CD4 testing has been cited as a key barrier in the HIV care cascade, leading to delays in antiretroviral treatment (ART) initiation. Point-of-care (POC) CD4 testing has been demonstrated to improve linkage to care (LTC) among HIV-seropositive persons, but its impact has not been assessed with a randomized, controlled trial (RCT) in the context of home-based HIV counseling and testing (HBCT). We evaluated whether providing POC CD4 count, integrated with HBCT and referral for HIV care, would improve LTC and ART initiation when compared to standard-of-care (SOC) lab-based CD4 measurement.

Methods: RCT participants were enrolled July'13-Feb.'14 in two districts of Western Kenya with ongoing HBCT. Compounds were randomized 1:1 to POC CD4 (Alere PIMA) or SOC CD4 testing at one of three referral labs. Participants in both arms received HBCT, post-test counseling, and referral for HIV care. All HIV+ adults not engaged in care in last 180 days were invited to participate. Intervention arm participants received additional counseling on the POC CD4 result, including ART eligibility if CD4<350cells/μL. Enrolled participants gave informed consent. Participants were interviewed 180 days after enrollment to ascertain whether and where they sought care, which was verified with charts at any of 23 clinics serving the study area. Verified LTC (a HIV clinic visit) was primary outcome, with protocol-specified analysis of time to ART initiation comparing SOC to intervention using a Cox proportional hazards model.

Results: We describe final results from 770 enrolled participants, of whom 692 had chart-verified LTC status, and 78 were lost to followup. Baseline characteristics including sex, age, education, marital and employment status were similar in the two arms. Of 321 SOC participants, 106 (33.0%) had confirmed LTC within 180 days after enrollment, whereas of 371 in intervention arm, 208 (56.1%) had confirmed LTC (HR = 1.996; 95%CI: 1.58-2.52). Kaplan-Meier analysis of time to LTC (Figure) produced a log-rank p<0.0001 for the difference in proportions linked to HIV care in two arms. Among SOC participants, 33 (10.3%) had initiated ART, compared to 61 (16.4%) in the intervention arm (HR = 1.67; 95%CI: 1.09-2.55).

Figure: Kaplan-Meier analysis of time to linkage to care by randomized clinical trial arm, Western Kenya, 2013-2014



^SOC=Standard of Care (referral lab CD4);
*POC=Point of Care CD4

Kaplan-Meier analysis revealed a significant, early and durable impact of point of care CD4 testing compared to referral lab CD4 testing, on proportion linked to care after home-based HIV testing.

Conclusions: Final results of the first RCT on the impact of POC CD4 testing in a resource-limited HBCT setting revealed significant improvements in rate of LTC and ART initiation. Further analyses on time to ART initiation, and predictors of LTC and ART initiation, are ongoing.

633 Reliable Genotypic Tropism Tests for the Major HIV-1 Subtypes

Kieran Cashin[1]; Lachlan R. Gray[1]; Katherine L. Harvey[1]; Danielle Perez-Bercoff[2]; Guinevere Q. Lee[3]; Jasminka Sterjovski[1]; James F. Demarest[4]; Fraser Drummond[4]; Melissa J. Churchill[1]; Paul R. Gorry[1]
[1]Burnet Institute, Melbourne, Australia; [2]Centre Recherche Public de la Santé, Strassen, Luxembourg; [3]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; [4]ViiV Healthcare, Durham, NC, US

Background: The major obstacles to the CCR5-antagonist maraviroc being more widely used in anti-HIV-1 therapy regimens are (i) traditional pre-treatment phenotypic tropism tests to determine virus susceptibility to maraviroc are expensive and time consuming, and (ii) cheaper and more rapid genotypic tropism tests have been developed primarily for HIV-1 subtype B strains, which account for only 10% of infections worldwide. We therefore developed PhenoSeq, a suite of reliable genotypic tropism tests specific for HIV-1 subtypes A, B, C, D and circulating recombinant forms of subtypes AE (CRF01_AE) and AG (CRF02_AG), which together account for 95% of infections worldwide.

Methods: Development of subtype-specific genotypic tropism tests was informed by analysis of all HIV-1 *env* third variable region (V3) amino acid sequences from the Los Alamos HIV Database that had corresponding phenotypic tropism and HIV-1 subtype data (n=2257; 630 CXCR4-using and 1637 CCR5-using), to elucidate statistically significant sequence alterations that distinguish CXCR4- from CCR5-using viruses. With the aid of a new bioinformatic tool that we developed (bulk2clonal), PhenoSeq algorithms were validated against independent clinical HIV-1 sequence panels from patients previously enrolled in the Pfizer trials A4001064 and MERIT, relative to results of the original Trofile assay (OTA) and the enhanced sensitivity Trofile assay (ESTA).

Results: Our analyses show that the PhenoSeq genotypic algorithms exhibit more favourable sensitivity and specificity profiles for establishing the tropism of HIV-1 subtypes A, B, C, D, CRF01_AE and CRF02_AG than current alternative algorithms, including the clinically validated in-use algorithms geno2pheno (g2p; false positive rate 5.75% and 10%) and WebPSSM (Table 1). Furthermore, PhenoSeq area under the receiver operator characteristic curves (AUROC) were significantly greater than g2p FPR 5.75% for establishing the tropism of HIV-1 subtype C (p=0.01), g2p FPR 10% for CRF01_AE (p=0.03), and WebPSSM for subtypes B (p=0.01) and D (p=0.05) (two-tailed t-test, p≤0.05 considered significant).

Performance of genotypic tropism tests against independent V3 sequences

		PhenoSeq	g2p FPR 5.75%	g2p FPR 10%	$WebPSSM_{X4R5}$	$WebPSSM_{SI/NSI}$
B-HIV Test Set 1 OTA 12 CXCR4-using, 41 R5	**Sens/Spec**	100/87.8	100/97.6	100/90.2	41.7/95.1	16.7/87.8
	AUROC	0.94	0.99 (p=0.17)	0.95 (p=0.44)	0.68 (**p=0.01**)	0.52 (**p=0.01**)
B-HIV Test Set 2 LANL 92 CXCR4-using, 269 R5	**Sens/Spec**	78.4/80.3	70.7/92.2	72.8/84	55.4/96.3	62/94.1
	AUROC	0.79	0.82 (p=0.32)	0.78 (p=0.41)	0.76 (p=0.24)	0.78 (p=0.41)
C-HIV Test Set 1 OTA 55 CXCR4-using, 40 R5	**Sens/Spec**	83.6/92.5	78.2/95	81.8/95	-	85.5/77.5
	AUROC	0.88	0.87 (p=0.22)	0.88 (p=0.30)	-	0.82 (p=0.22)
C-HIV Test Set 2 ESTA 18 CXCR4-using, 187 R5	**Sens/Spec**	77.8/75.4	11.1/93	50/82.4	-	61.1/81.3
	AUROC	0.77	0.52 (**p=0.01**)	0.66 (p=0.15)	-	0.71 (p=0.29)
D-HIV Test Set OTA 43 CXCR4-using, 44 R5	**Sens/Spec**	80.5/77.3	81.4/72.7	88.4/61.4	81.4/65.9	69.8/63.6
	AUROC	0.79	0.77 (p=0.40)	0.75 (p=0.29)	0.74 (p=0.24)	0.67 (**p=0.05**)
CRF01_AE Test Set OTA 14 CXCR4-using, 25 R5	**Sens/Spec**	85.7/96	78.6/68	85.7/56	85.7/72	85.7/76
	AUROC	0.91	0.73 (**p=0.046**)	0.71 (**p=0.03**)	0.79 (p=0.11)	0.81 (p=0.15)
CRF02_AG Test Set 1 OTA 9 CXCR4-using, 69 R5	**Sens/Spec**	88.9/76.8	44.4/97.1	55.6/94.2	44.4/87	66.7/84
	AUROC	0.83	0.71 (p=0.18)	0.75 (p=0.27)	0.66 (p=0.10)	0.75 (p=0.28)
CRF02_AG Test Set 2 OTA 8 CXCR4-using, 36 R5	**Sens/Spec**	62.5/97.2	50/94.4	62.5/80.6	37.5/88.9	37.5/91.7
	AUROC	0.80	0.72 (p=0.30)	0.72 (p=0.29)	0.63 (p=0.14)	0.65 (p=0.16)

Sens, % sensitivity was calculated by dividing the number of correctly predicted CXCR4-using sequences by the total number CXCR4-using sequences and multiplying by 100. Spec, % specificity was calculated by dividing the number of correctly predicted R5 sequences by the total number of R5 sequences and multiplying by 100. P-values (two-tailed) for comparisons of area under the receiver operator characteristic curve (AUROC) <0.05 were considered significant and are highlighted in bold text. g2p, geno2pheno. OTA, original Trofile assay. ESTA, enhanced sensitivity Trofile assay. LANL, Los Alamos HIV Database. FPR, false positive rate. *The subtype C specific WebPSSMSI/NSI algorithm was used for subtype C HIV-1 predictions.

Conclusions: As the only platform of algorithms that can reliably infer the tropism of the major global HIV-1 subtypes, PhenoSeq has the potential to inform the appropriate use of maraviroc and future CCR5 blocking drugs in regions of the world where non-B HIV-1 predominates, and which are burdened the most by the HIV-1 pandemic.

634 Accuracy of Re-Reading HIV Rapid Tests and the Effect of Prolonged High Temperature

Augustine T. Choko[1]; Deus Thindwa[1]; Peter MacPherson[2]; Rodrick Sambakunsi[1]; Aaron Mdolo[1]; Kondwani Chiumya[1]; Owen Malema[3]; Simon Makombe[4]; Emily L. Webb[6]; **Elizabeth L. Corbett**[6]

[1]Malawi Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi; [2]University of Liverpool, Liverpool, United Kingdom; [3]Ministry of Health, Blantyre, Malawi; [4]Ministry of Health, Lilongwe, Malawi; [5]London School of Hygiene and Tropical Medicine, London, United Kingdom; [6]London School of Hygiene and Tropical Medicine, London, United Kingdom

Background: Accurate rapid diagnostic test (RDT) results are critical to HIV testing, care and prevention services. However, suboptimal storage at ambient temperatures above manufacturer-recommendation is common in sub-Saharan Africa. Re-reading of used test kits can provide valuable programmatic quality-assurance, and "late" reading is also commonly reported following HIV self-testing. We evaluated the effects of prolonged exposure to high temperatures on both initial accuracy, and reproducibility of late reads.

Methods: A cross-sectional diagnostic evaluation in Blantyre, Malawi. Consenting participants attending HIV testing services had parallel testing with 3 RDTs (OraQuick (oral), Determine 1/2™, Alere, Waltham, USA and Uni-Gold™ Recombigen® HIV, Trinity Biotech, Bray, Ireland): a) preincubated for 28 days at 37 ○C as intact packages and b) the same 3 RDTs stored under optimal conditions (6 tests in total). All 6 kits were read by the study nurse at the recommended time, and then again by a laboratory technician on the same day and monthly for 12 months (although with reference to previous results). Optimally stored Uni-Gold/Determine/SD Bioline were used for the gold standard.

Results: Of 378 participants, 198 (53.4%) were male with median age 31 years (IQR 25-40). Compared to gold standard, sensitivity for normal and high temperature OraQuick, Determine and Uni-Gold are shown in the table below. All but 6 participants had concordant results from each of the 6 kits, with no discernable effect on accuracy from preincubation. One participant was positive on both OraQuick (optimal) and Determine (optimal), but negative on the other RDTs, and was classified as HIV-negative. A further 5 participants had false-negative results on one or more RDTs. Notably, 108 (28.6%) reported being on antiretroviral treatment (ART). Over 12 months of re-reading used OraQuick kits; 1 (0.3%) in both optimal-stored and high temperature groups changed from negative to positive (different clients). In both cases participants were known to be on ART.

Sensitivity and specificity for rapid diagnostic HIV kits stored in prolonged high temperature (37 deg C) and optimal temperature

Type of rapid test kit	TP/FN	Sensitivity (95% CI)	TN/FP	Specificity (95% CI)
Normal temperature OraQuick	177/3	98.3 (95.2-99.7)	186/1	99.5 (97.1-100)
High temperature OraQuick	178/5	97.3 (93.7-97.3)	190/0	100 (98.1-100)
Normal temperature Determine	182/2	98.9 (96.1-99.9)	189/1	99.5 (97.1-100)
High temperature Determine	182/2	98.9 (96.1-100)	189/1	99.5 (97.1-100)
Normal temperature Uni-Gold	183/1	99.5 (97.0-100)	192/0	100 (98.1-100)
High temperature Uni-Gold	182/2	98.9 (96.1-100)	189/0	100 (97.1-100)

CI: confidence interval; TP: true positive; FN: false negative; TN: true negative; FP: false positive

Conclusions: This study showed that rapid diagnostic HIV test kits stored at prolonged high temperature did not appreciably affect diagnostic performance. Repeated reading of OraQuick kits up to 12 months after testing appears to be highly reproducible, although not recommended by the manufacturer. Clients seeking retesting while on ART maybe an increasing common cause of inaccuracy in HTC clinics.

635 Analysis of False Negative HIV Tests Based on Oral Fluid in 3 Clinical Trials

Marcel E. Curlin[1]; Michael T. Martin[1]; Wanna Leelawiwat[2]; Roman Gvetadze[1]; Charles Rose[1]; Sarika Pattanasin[2]; Richard Niska[1]; Timothy Holtz[1]; Kachit Choopanya[3]; Janet McNicholl[1]

[1]US Centers for Disease Control and Prevention, Apo, US; [2]Thailand Ministry of Public Health–Centers for Disease Control and Prevention Collaboration, Nonthaburi, Thailand; [3]Bangkok Tenofovir Study Group, Bangkok, Thailand

Background: The OraQuick Advance Rapid HIV-1/2 Antibody Test (OraSure, Bethlehem, PA) is a non-invasive, point-of-care, rapid HIV test capable of detecting HIV-specific antibodies in blood and oral fluid. The test is convenient and promises to increase HIV testing in at-risk populations. However, concerns regarding test sensitivity in oral fluid suggest that OraQuick Oral fluid (OQOF) test performance should be further studied before relying on this assay in clinical trials and other contexts where negative predictive value may be lower than in typical clinical settings.

Methods: We examined OQOF performance among all seroconverting participants in the Botswana Tenofovir PrEP Study (TDF2), the Bangkok Tenofovir Study, and the Bangkok Men Who Have Sex With Men Cohort Study, three longitudinal clinical studies conducted in Botswana and Thailand. OQOF screening test results were compared with estimated time of infection determined by enzyme immunoassay and/or nucleic acid amplification tests on stored blood samples. We used generalized estimating equations log-binomial regression to examine the association between FN OQOF test results and participant age and gender, time since infection, viral subtype, plasma viral load (PVL), exposure to antiretroviral drugs, test operator, clinical site, and test lot.

Results: In total, we identified 208 false negative (FN) OQOF test results among 81 of 290 (28%) seroconverters (all studies). Median estimated OQOF reactivity delay time was 98 days (range 14-547 days). FN tests were correlated with testing within 90 days of estimated date of infection, randomization to ARV-based pre-exposure prophylaxis, lower plasma viral loads, individual test operators, and specific testing sites, in one or more studies ($p < 0.05$). Age, gender, HIV subtype and test kit lot were not associated with FN tests ($p > 0.05$).

Conclusions: Failure of OQOF to detect HIV-1 infection was frequently observed in these three studies. Factors contributing to FN OQOF test results include recent infection, exposure to antiretroviral agents, low PVL, and operator-related factors. In the context of clinical trials, where a FN test may be more likely than in routine clinical settings, negative screening tests based on oral fluid should be confirmed by laboratory-based tests in blood, and measures should be taken to ensure proper training and ongoing quality assurance.

TUESDAY, FEBRUARY 24, 2015

Session P-N1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Natural History and Prognosis of HCV Infection

636 Progression of Liver Disease in LHIV/HCV Coinfected People According to Gender in Icona Cohort: Role of Age as Potential Different Exposure to Estrogens

Antonella Cingolani[1]; Paola Cicconi[2]; Gloria Taliani[3]; Alessandro D. Cozzi-Lepri[4]; Massimo Puoti[5]; Carmela Pinnetti[6]; Pier Luigi Viale[7]; Antonella d'Arminio Monforte[2]
for Icona Foundation Study Group

[1]Catholic University, Roma, Italy; [2]University of Milano, Milano, Italy; [3]University La Sapienza, Roma, Italy; [4]University College London Medical School, Royal Free Campus, London, United Kingdom, London, United Kingdom; [5]Niguarda Hospital, Milano, Italy; [6]National Institute for Infectious Diseases L. Spallanzani, Roma, Italy; [7]Univeristy of Bologna, Bologna, Italy

Background: In HCV patients, female gender was reported as protective in liver fibrosis progression. However, post menopausal women show an increased rate of progression, suggesting a causative role of estrogens. Aim of the study was to evaluate the effect of age (proxy of menopausal status), on liver disease progression in a large HIV/HCV population.

Methods: All patients (pts) enrolled in the ICONA Foundation study with at least 1 HCVAb+ test available were included. Predictors of liver fibrosis (FIB-4>3.25) at baseline (first HCVab+ test available) were identified by logistic regression (gender; age, risk factor for HIV HBsAg, HCV genotype, CD4, baseline HIV RNA, years from HIV diagnosis, calendar year of enrollment). The effect of aging was examined by comparing Fib4 trends before and after age 50 in men and women, using a two-piecewise random coefficient model.

Results: 2833 pts were examined: 739 (26%) women, median age 36 y (IQR 33-40), 6 years from HIV diagnosis (IQR 1-11), median CD4/ml 410 (IQR 221-600). Overall, 15.4% showed liver fibrosis at baseline, with a significantly lower proportion in females when compared to men (11% vs. 17%, p=<.0001). However after adjusting for potential confounders, the protective role of female gender on fibrosis was not confirmed (female AOR 0.8, 95%CI 0.4-1.3). Older age (AOR 2.0, 95%CI 1.4-2.8, +10 years), HBsAg+ (AOR 3.3, 95%CI 1.3-7.9), IVDU (AOR 1.8, 95%CI 1.0-3.4) and CD4 count (AOR 0.9, 95%CI 0.8-0.9 +100 cells/ml) were predictors of fibrosis at baseline. For the analysis of trends, 45498 FIB-4 measurements were analyzed. Median FIB-4 at enrollment was 1.15 (IQR 0.77-1.88) in women and 1.53 (IQR 0.98-2.58) in men (Wilcoxon test p<.0001). In females, FIB-4 did not significantly change before (estimate 0.13/10 y, p=.47) or after 50 y (estimate 0.13/10 y, p=.38) and no change in trend is observed (difference .006, p=.97). In males, FIB4 significantly increased after 50 y (estimate 0.11/10 years, p=.009); but no change in trend before and after the age cut-off was found (difference in trend 0.04, p=.31).

Conclusions: Differently from what reported for HCV monoinfected female population, fibrosis progression in HIV/HCV females seems to be a quite linear phenomenon similar to what observed in the male counterpart. This finding suggests the pathogenetic relevance of potential pathways to inflammatory process other than estrogens deprivation in HIV/HCV coinfected women

637 A Prognostic Score Estimating the Risk of Liver-Related Death Among HIV/HCV Coinfected Subjects

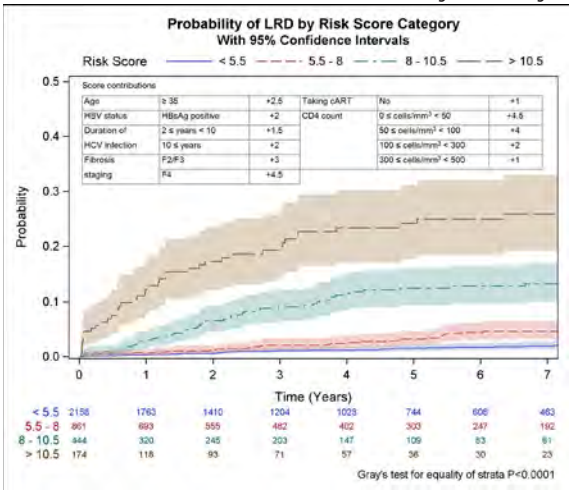
Daniel Grint[1]; Lars Peters[2]; Jürgen Rockstroh[3]; Karine Lacombe[4]; Andrzej Horban[5]; Irina Khromova[8]; Jose Gatell[6]; Antonella d'Arminio Monforte[7]; Jens D. Lundgren[2]; **Amanda Mocroft**[1]
on behalf of EuroSIDA in EuroCoord

[1]University College London, London, United Kingdom; [2]University of Copenhagen, Copenhagen, Denmark; [3]University Hospital Bonn, Bonn, Germany; [4]Hospital Saint Antoine, Paris, France; [5]Wojewodzki Szpital Zakazny, Warsaw, Poland; [6]University of Barcelona, Barcelona, Spain; [7]Clinica delle Malattie Infettive e Tropicali, Milan, Italy; [8]Centre for HIV/AIDS & Infectious Diseases Prevention & Control, Kaliningrad, Russian Federation

Background: Development of a simple, widely applicable prognostic score for liver-related death (LRD) among HIV/HCV coinfected individuals is essential to predict the future burden of LRD. An accurate prognostic score in this setting will aid comparison of individual risk profiles when prioritising who should be treated with new directly-acting antivirals for HCV.

Methods: EuroSIDA patients with HCV coinfection and follow-up after 1/1/2000 were included. Causes of death were classified using CoDe methodology. Fibrosis staging is estimated from liver biopsy, Fibroscan®, APRI and hyaluronic acid. Competing risks Cox proportional hazards modelling with stepwise variable selection was used to identify factors associated with long term risk of LRD. Scaled model coefficients were used to create a prognostic score for LRD.

Results: 669 deaths were recorded (159 liver-related) from 3637 coinfected individuals during 14613 PYFU to November 2013. The study population was mostly Caucasian (94%), male (68%), injecting drug users (71%). At baseline the majority had F0/F1 fibrosis (76%), followed by F2/F3 (15%) and F4 (9%). Factors associated with LRD that contribute to the prognostic score are age, CD4 cell count, liver fibrosis stage, HBV coinfection, known duration of HCV infection and cART status (**Figure 1**). The overall mean score was 5.0 (95% CI 4.9-5.1), but significantly higher among those who died of LRD (8.1 (7.6-8.6)), $P<0.0001$. A 1-unit increase in the score is associated with 2.6-fold increased risk of LRD (Hazard ratio: 2.6 (2.3-3.0; $P<0.0001$)). Increasing CD4 cell count from 100-300 cells/mm^3 to >500cells/mm^3 is associated with a 6.8-fold (5.1-9.0) reduced risk of LRD. Prediction of LRD based solely on fibrosis staging achieved an area under the ROC curve (AUROC) of 0.71, whereas the score achieved an AUROC of 0.83. A score cut-off of 6.5 provided the highest combination of sensitivity (71.1%) and specificity (83.1%). The 5-year probability of LRD increased from 1.6% (1.0-2.2) in those at low risk to 3.2% (2.1-4.8), 12.5% (9.4-16.2) and 24.2% (17.8-31.0) in those at medium-low risk, medium-high risk and high risk of LRD respectively, $P<0.0001$ for separation between strata (**Figure 1**).



Conclusions: A simple prognostic score calculated from information readily collected at clinical centres can accurately predict progression to LRD among HIV/HCV coinfected individuals. The score outperformed prediction based solely on fibrosis staging highlighting the importance of the other clinical elements.

638 Has Modern ART Reduced Endstage Liver Disease Risk in HIV-Hepatitis Coinfection?

Marina B. Klein[1]; Keri N. Althoff[3]; Yuezhou Jing[3]; Greg D. Kirk[3]; Vincent Lo Re[2]; Nina Kim[4]; Mari Kitahata[4]; Chloe Thio[3]; Michael J. Silverberg[5]; Richard Moore[3]
North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)

[1]McGill University Health Centre, Montreal, Canada; [2]University of Pennsylvania, Philadelphia, PA, US; [3]Johns Hopkins University, Baltimore, MD, US; [4]University of Washington, Washington, DC, US; [5]Kaiser Permanente Northern California, Oakland, CA, US

Background: HIV-infected adults are commonly coinfected with hepatitis B (HBV) and C (HCV) viruses and thus at risk for Endstage Liver Disease (ESLD). Whether safer, more effective modern ART has reduced ESLD rates is unknown. We estimated ESLD incidence since the introduction of combination ART by HBV and HCV co-infection status in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

Methods: HIV-infected adults participating in the 12 cohorts contributing to the NA-ACCORD who were observed for validated ESLD diagnoses from Jan 1, 1996 to Jan 1, 2010 were included. HBV was defined by a positive surface or e antigen test or detectable HBV DNA. HCV was defined as a positive antibody test or detectable HCV RNA. ESLD events (ascites, SBP, bleeding varices, encephalopathy, hepatoma) were validated using standardized screening and review protocols. Poisson regression models were used to estimate incidence rates (IR, per 1,000 p-years) and ratios (adjusted for age, sex, race and cohort; aIRR) with 95% confidence intervals ([,]) in the early (1996-2000), middle (2001-2005) and modern (2006-2010) ART eras.

Results: 34,119 adults contributed 380 incident ESLD outcomes and >129,000 person-years. Overall, ESLD incidence was similar in the early, middle and modern ART eras. In all three eras, incidence rates were highest in HIV/HCV/HBV and lowest among HIV monoinfected with HIV/HCV/HBV having the highest aIRRs (see Table). No significant change in rates of ESLD was observed across the 3 time periods for any group. Comparing the early vs. modern eras, aIRR [95% CI] were: 1.6[0.8, 3.4]; 1.3[0.8, 2.1] and 0.5 [0.1, 1.9] for HIV/HCV, HIV/HBV and HIV/HCV/HBV respectively. Similarly, comparing middle vs. modern eras, aIRR [95% CI] were: 1.1[0.7, 1.6], 0.8[0.6, 1.2] and 0.5[0.2, 1.2]. Overall death rates were high in the early ART era which may have lead to an underestimation of ESLD risk in this period. However, death rates were similar in the middle and modern eras.

			N	ESLD events	Person years	Incidence rate/ 1000 person-yrs (95% CI)	Adjusted Incidence ratio (95% CI)[a]
Early ART era (1996-2000)	OVERALL		10395	69	22408	3.08 (2.43, 3.9)	n/a
	Hepatitis Status	HIV only[b]	4892	12	10179	1.18 (0.67, 2.08)	ref
		HIV/HCV[c]	2575	39	6462	6.04 (4.41, 8.26)	8.2 (4.1, 16.3)
		HIV/HBV[d]	466	8	972	8.23 (4.12, 16.46)	7.5 (3, 18.5)
		HIV/HCV/HBV[e]	189	5	500	9.99 (4.16, 24.01)	12.9 (4.3, 38.1)
Middle ART era (2001-2005)	OVERALL		21188	178	60178	2.96 (2.55, 3.43)	n/a
	Hepatitis Status	HIV only	11132	42	32035	1.31 (0.97, 1.77)	ref
		HIV/HCV	4201	73	12989	5.62 (4.47, 7.07)	5.3 (3.5, 8)
		HIV/HBV	1076	31	3181	9.75 (6.85, 13.86)	8.9 (5.6, 14.3)
		HIV/HCV/HBV	362	11	1185	9.28 (5.14, 16.76)	10.4 (5.3, 20.7)
Modern ART era (2006-2010)	OVERALL		22472	133	47232	2.82 (2.38, 3.34)	n/a
	Hepatitis Status	HIV only	14335	38	30262	1.26 (0.91, 1.73)	ref
		HIV/HCV	4026	61	8891	6.86 (5.34, 8.82)	6.9 (4.5, 10.6)
		HIV/HBV	1074	17	2267	7.5 (4.66, 12.06)	5.9 (3.3, 10.6)
		HIV/HCV/HBV	298	11	648	16.97 (9.4, 30.65)	17.9 (8.9, 36)

Note: [a] incidence rate ratios adjusted for age (<40, 40-49, 50-59, 60-69. >=70), sex, race and cohort;
[b] HIV only was defined as HBV negative and HCV negative;
[c] HIV/HCV only was defined as HCV positive and (HBV negative or HBV not assessed);
[d] HIV/HBV was defined as HBV positive and (HCV negative or HCV not assessed);
[e] HIV/HCV/HBV was defined as HBV positive and HCV positive.

Table. Incidence of ESLD by ART Era and Hepatitis Status in the NA-ACCORD

Conclusions: Hepatitis virus co-infected adults are at markedly increased risk for ESLD compared those infected with HIV alone, with triply infected patients at greatest risk. No clear reduction in ESLD risk was observed over the three time periods. The continued high incidence of ESLD despite modern ART underscores the urgent need to specifically address HCV and HBV infections in HIV infected adults.

639 Marijuana Use Does Not Accelerate Liver Fibrosis in HCV/HIV-Coinfected Women

Erin M. Kelly[1]; Jennifer L. Dodge[1]; Monika Sarkar[1]; Audrey French[2]; Phyllis Tien[1]; Marshall Glesby[3]; Elizabeth Golub[4]; Michael Augenbraun[5]; Michael Plankey[6]; **Marion G. Peters**[1]
WIHS

[1]University of California San Francisco, San Francisco, CA, US; [2]CORE Center/Stroger Hospital, Chicago, IL, US; [3]Weill Cornell Medical College, New York City, NY, US; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [5]State University of New York, Downstate Medical Center, Brooklyn, NY, US; [6]Georgetown University, Washington, DC, US

Background: Cannabis (THC) use has been correlated with liver fibrosis progression in retrospective analyses of mono-infected chronic hepatitis C (HCV) patients, particularly in those with established fibrosis. We studied long-term effects of THC on fibrosis progression in women co-infected with HCV/HIV enrolled in Women's Interagency HIV Study (WIHS), a prospective, multicenter, cohort of women with or at risk for HIV infection.

Methods: Liver fibrosis was categorized according to APRI scores as mild (<0.5), moderate (0.5-1.5), or severe (≥1.5): women with severe fibrosis at entry into WIHS were excluded. THC and alcohol use were treated as continuous variables and quantified as average exposure over time in study until last follow-up or development of severe fibrosis. Associations between THC use and progression to severe fibrosis were assessed using Cox proportional hazards regression.

Results: Among 670 HIV/HCV co-infected women (median follow-up: 5.1 (1.2-10.5) years), 323 (49%) reported no THC use; 209 (31%) reported ≥weekly use; 134 (20%) ⟨weekly use; and 4 no THC data. Median APRI at entry were similar (0.53 vs 0.49 vs 0.50) in those who reported no THC use, ⟨weekly use and ≥ weekly use, respectively. Compared to women

reporting no THC use, weekly users reported more injection drug [28% vs 18% p=0.004] and alcohol use [60% vs 44% p=0.001]. In univariate analysis, log APRI [HR 10.35 (5.69-18.84) p<0.001], log HCV RNA [HR 1.3 (1.10-1.54) p=0.002] and log HIV RNA [HR 1.14 (1.02-1.29) p=0.03] at entry were associated with progression to severe fibrosis; higher CD4+ count [per 50 cells HR 0.96 (0.93-0.98) p<0.0004] and ART use [HR 0.62 (0.38-1.01), p=0.05] were associated with lower fibrosis. Cumulative alcohol use [risk per 1 drink increase per week [HR 1.03 (1.02-1.04) p<0.001] was associated with greater risk of progression. In multivariate analysis, entry APRI, HCV RNA, CD4+ count and cumulative alcohol use remained significant. Cumulative THC use was not independently associated with a greater risk of fibrosis progression [HR 1.00 (95% CI 0.996-1.003)] even in those with moderate fibrosis at entry [HR 1.00 (95% CI 0.995-1.005)].

Conclusions: In this large cohort of HCV/HIV co-infected women with prospectively collected cumulative alcohol and THC use, THC was not associated with liver fibrosis progression. Interestingly, alcohol use was strongly associated with THC use and independently associated with liver fibrosis, and may better predict fibrosis progression in HCV/HIV co-infected women

640 HIV Infection Does Not Worsen Prognosis of Liver Transplantation for Hepatocellular Carcinoma

Fernando H. Agüero[1]; Alejandro Forner[2]; Christian Manzardo[1]; Andres Valdivieso[3]; Marino Blanes[4]; Rafael Barcena[5]; Antoni Rafecas[1]; Lluis Castells[6]; Antonio Rimola[1]; Jose M Miro[1]

[1]University of Barcelona, Barcelona, Barcelona, Spain; [2]Hospital Clinic, IDIBAPS and El Centro de Investigación Biomédica en Red en el Área Temática de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; [3]Hospital Universitario de Cruces, Bilbao, Spain, Bilbao, Spain; [4]Hospital Universitario La Fe, Valencia, Spain, Valencia, Spain; [5]Hospital Universitario Ramón y Cajal, Madrid, Spain, Madrid, Spain; [6]Hospital Universitari Vall d'Hebrón, Barcelona, Spain, Barcelona, Spain

Background: Small series of liver transplantation (LT) in HIV-infected patients with hepatocellular carcinoma (HCC) have been reported in recent years. However, data on recurrence of HCC and survival after LT are limited and controversial. The aim of this study was to assess the impact of HIV on clinical outcome in patients undergoing LT for HCC.

Methods: Prospective cohort study of HIV-infected patients with HCC who received LT at 22 Spanish centres (FIPSE cohort) and were matched with non–HIV-infected LT recipients (1:3 ratio). The study started in 2002, and follow-up ended in July 2014. The matched criteria were age, gender, calendar year of LT, HCV or HBV coinfection, and HCC. The main outcomes were recurrence of HCC and survival. Patients with incidental HCC were excluded.

Results: In total, 74 HIV-infected patients and 222 non–HIV-infected patients underwent LT for HCC. Most were men (86%) and had HCV infection (92%). HIV-infected patients were younger (47 vs 51 y) and the frequency of HCV replication at LT was lower (80% vs 90%) than in HIV-negative patients. At LT, median (IQR) CD4 cells/mm^3 was 347 (238-523) and most HIV-infected patients (96%) were on antiretroviral therapy. HIV plasma viral load was <50 copies/mL in 93%. No differences were seen between HIV-infected and non–HIV-infected recipients in the pathological characteristics of HCC in the explanted liver (**Table**). After a median of 46 (25-72) months of follow-up, recurrence was recorded in 12 (16%) HIV-infected patients and 32 (14%) HIV-negative patients, Recurrence at 1, 3, and 5 years (Kaplan-Meier estimates) for HIV-infected patients vs non–HIV-infected patients was 7% vs 5%, 17% vs 11%, and 20% vs 19%, respectively (p=0.876), with a similar rate of recurrence: 0.229 and 0.266 person-year, respectively. The incidence rate ratio was 0.86 (95% CI, 0.66-1.12). In the whole series, microscopic vascular invasion (HR, 3.79 95% CI, 1.67-8.57) was the only factor independently associated with recurrence of HCC. Survival at 1, 3, and 5 years for HIV-infected patients vs non–HIV-infected patients was 87% vs 89%, 78% vs 78%, and 69% vs 73% (p=0.905). HCV infection (HR, 8.85 95% CI, 1.23-63.64) and satellite nodules (HR, 1.92 95% CI, 1.13-3.24) were the variables independently associated with mortality.

Table. Pathological features and follow-up characteristics of liver transplant patients with Hepatocelullar carcinoma (HCC) . Spanish cohort (2002-2012)

	Total N=296	HIV+ N=74	HIV- N=222	*P*-value
Pathological features n, (%) - Single nodule - Multiple nodules	 129 (44) 162 (56)	 31 (43) 41 (57)	 98 (45) 121 (55)	0.802
Maximum nodule diameter	2.5 (2;3.2)	2.5 (2;3.2)	2.6 (2;3.2)	0.978
Microscopic vascular invasion	47 (16)	16 (22)	31 (14)	0.114
Macroscopic vascular invasion	10 (3)	1 (1)	9 (4)	0.265
Satellite nodules	36 (13)	7 (10)	29 (13)	0.453
- Outside Criteria	71 (25)	18 (25)	53 (25)	0.985
- Outside UCSF Criteria	49 (18)	13 (18)	36 (17)	0.874
Median follow-up time, months	46 (25;72)	48 (31;78)	44 (24;71)	0.186
HCC recurrence n, (%)	44 (15)	12 (16)	32 (14)	0.706
- Intrahepatic	6 (2)	2 (3)	4 (2)	0.629
- Extrahepatic	22 (7)	7 (9)	15 (7)	
- Both	16 (5)	3 (4)	13 (5)	
Interval LT-HCC recurrence, months	22 (11;38)	22 (11;42)	22 (11;34)	0.541
Crude Mortality n, (%)	88 (30)	24 (32)	64 (29)	0.557
HCC-related Mortality n, (%)	23 (8)	6 (8)	17 (8)	0.882

Conclusions: HIV-infection did not have any impact on recurrence of HCC or survival after LT. These results support the indication of LT in HIV-infected patients with HCC.

641 Rapid Progression to Cirrhosis and Death Among HCV-Infected Persons Who Inject Drugs in India

Shruti H. Mehta[1]; Suniti Solomon[2]; Allison M. McFall[1]; Aylur K. Srikrishnan[2]; Pachamuthu Balakrishnan[2]; Nandagopal P[2]; David L. Thomas[1]; Mark Sulkowski[1]; Sunil S. Solomon[1]

[1]Johns Hopkins University, Baltimore, MD, US; [2]YR Gaitonde Centre for AIDS Research and Education, Chennai, India

Background: The recent introduction of direct-acting antivirals for HCV have sparked hope for HCV treatment in resource-limited settings (RLS). Despite WHO recommending HCV therapy for all chronically infected persons, it is likely that initially, similar to the early years of ART, access to these therapies will be limited in RLS. Therefore, it is critical to identify HCV-infected persons most in need of therapy.

Methods: A cohort of 809 persons who inject drugs (PWID) was recruited from 2/2012 – 9/2014 in Chennai, India, of whom 264 (34%) were chronically HCV-infected (HCV RNA positive). We characterized incidence of clinical outcomes (all cause-mortality and cirrhosis) among HCV-infected individuals with more than 1 follow-up visit (n=226). Cirrhosis was ascertained by elastography (Fibroscan) and all-cause mortality by verbal autopsy. Kaplan-Meier survival curves and Poisson regression were used to identify predictors. A subset was asked about barriers to accessing HCV treatment (n=57).

Results: Median age of HCV-infected persons was 42; all were male, 53% had primary school education or less and median monthly income was ~$97 USD. 84 (32%) were HIV/HCV co-infected. 51% had no fibrosis, 24% moderate fibrosis and 25% had severe fibrosis/cirrhosis at baseline. 57% had evidence of alcohol dependence by AUDIT. 27 died over

a median 1.5 years – mortality rate [MR]: 7.6 per 100 person-years (PY). Mortality per 100 PY was 4.7 among HCV mono-infected and 13.2 among HIV/HCV co-infected persons (adjusted incidence rate ratio [IRR]: 3.6; 95% confidence interval [CI]: 1.6-8.3; Figure). Mortality was also significantly higher in those with cirrhosis (IRR: 2.4; 95% CI: 1.1, 5.2; Figure) and those with alcohol dependence (IRR: 6.1; 95% CI: 2.5, 14.6). Among 151 without significant fibrosis/cirrhosis at baseline, 38 (25%) progressed to significant fibrosis/cirrhosis over a median of 1.5 years (IRR: 16.1 per 100 person-years). Overall, 6% reported being linked to care for hepatitis C, and 2% reported receiving treatment for hepatitis C with none achieving sustained virologic response. The primary reasons for not taking treatment were negative perceptions about treatment (e.g., side effects, low perceived efficacy; 60%) followed by cost (26%) and competing priorities (11%).

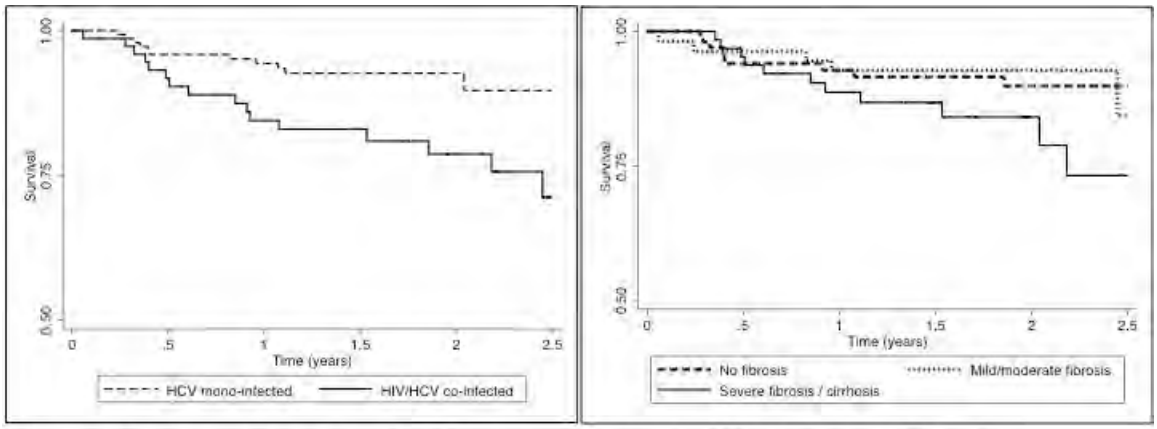


Figure. Kaplan-meier curves for all-cause mortality by HIV status and fibrosis

Conclusions: High mortality among HCV- and especially HIV/HCV-coinfected persons, low treatment uptake, and negative perceptions regarding interferon- based regimens underscore the importance of efforts to deliver all-oral HCV treatment in RLS.

642 Chronic Kidney Disease Progression After HCV Seroconversion

Adeel A. Butt

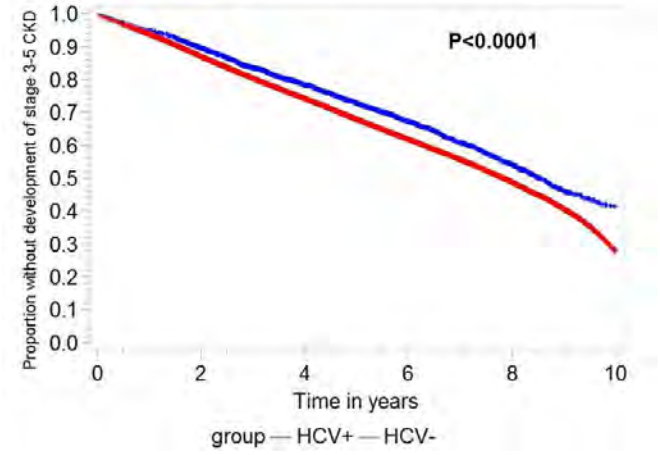
University of Pittsburgh/VA Pittsburgh Healthcare System, Pittsburgh, PA, US

Background: HCV infection has been associated with chronic kidney disease (CKD) progression and faster time to end stage renal disease. However, previous studies have been limited by lack of knowledge about timing of HCV infection and comparison with a comparable HCV uninfected population.

Methods: In a well-established national cohort of HCV infected Veterans (ERCHIVES), we identified persons with a known window for HCV seroconversion based on a negative initial and a subsequent positive HCV antibody test and a detectable HCV RNA. Controls had two negative HCV antibody tests in a comparable time frame. We excluded those with HIV coinfection, positive hepatitis B surface antigen and baseline stage 3-5 CKD. Among HCV seroconverted group, those who received HCV treatment were censored at time of treatment initiation. Glomerular filtration rate (GFR) was estimated using the CKD-EPI equation, and CKD was determined based on 2 GFR values ≥90 days apart. Primary outcomes were development of incident stage 3-5 CKD (GFR<60 mL/min/1.73 m^2) and progressive CKD (GFR decline ≥25% from baseline) among HCV seroconverted and uninfected groups.

Results: Final dataset consisted of 2,589 seroconverted and 68,939 HCV uninfected persons. Median age was 51 and 55 years, 71% and 56% were White and 94% and 96% were men in the seroconverted and uninfected groups respectively. Among seroconverted group, 19% had diabetes, 50% had hypertension and 34% received ACE-inhibitors or angiotensin receptor blockers (ACE-I/ARB). Among HCV uninfected, 25% had diabetes, 66% had hypertension and 47% received ACE-I/ARB. Median baseline GFR (mL/min/1.73 m^2) was 86.1 in HCV seroconverted and 82.6 in HCV uninfected group (P<0.0001). Stage 3-5 CKD developed in 37.3% of seroconverted and 33.8% of uninfected group (P=0.0003). Progressive CKD developed in 42.4% of seroconverted and 33.3% of uninfected group (P<0.0001). HCV seroconverted had faster time to development of CKD (figure), but progressive CKD (GFR decline ≥25%) was not different among groups.

Figure 1. Kaplan-Meier curves demonstrating time to development of stage 3-5 CKD over time, by HCV status.



Conclusions: This study provides new information about natural history of CKD among HCV seroconverted persons. HCV seroconverted persons were more likely to develop stage 3-5 CKD and accelerated time to incident stage 3-5 CKD. Interventions to decrease progression of CKD among HCV infected persons need further study.

TUESDAY, FEBRUARY 24, 2015

Session P-N2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HCV Therapy: Observations From Cohort Studies

643 Statins Improve SVR, Reduce Fibrosis Progression and HCC Among HCV+ Persons

Adeel A. Butt[1]; Peng Yan[2]; Obaid Shaikh[2]; Shari Rogal[2]

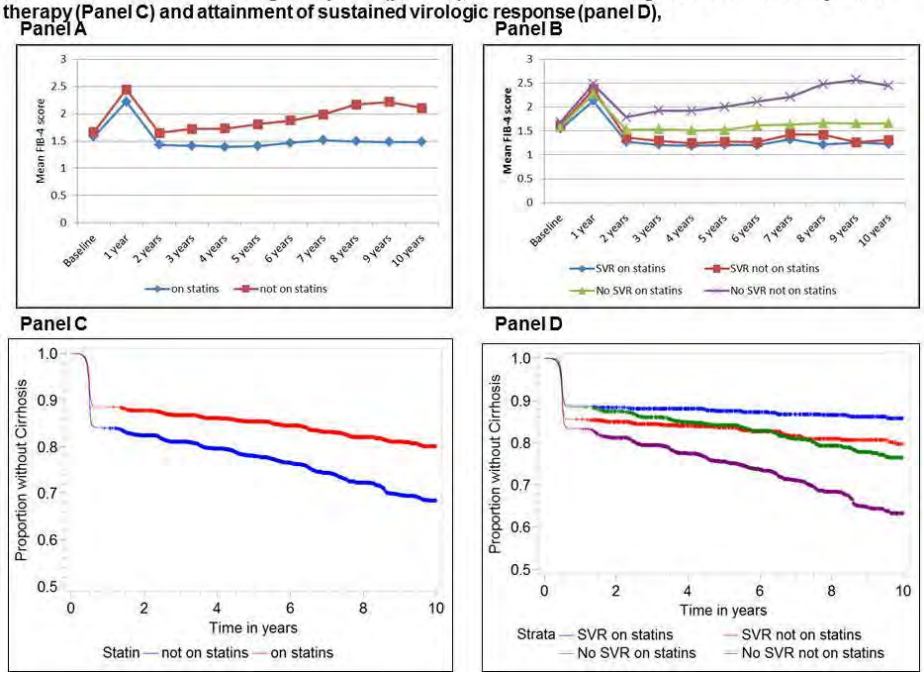
[1]*University of Pittsburgh/VA Pittsburgh Healthcare System, Pittsburgh, PA, US;* [2]*VA Pittsburgh Healthcare System, Pittsburgh, PA, US*

Background: Statins have been variably noted to affect HCV treatment response, fibrosis progression, and hepatocellular carcinoma (HCC) incidence. However, this has not been evaluated in a large national cohort while controlling for important confounders.

Methods: Within Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES), we identified those Veterans initiated on HCV treatment with a follow up of at least 24 months after treatment completion. We excluded those with HIV coinfection, hepatitis B surface antigen positivity, and those with missing data to determine SVR rates or FIB-4 score. Our main outcome measures were: 1) Liver fibrosis progression as measured by FIB-4 scores; 2) SVR rates, defined as proportion of participants with undetectable HCV RNA 12-48 weeks after completion of treatment; 3) incident HCC.

Results: Among 7,248 eligible subjects, 46% were taking statins. Statin use was significantly associated with attaining SVR (39.2% vs. 33.3%, p<0.01), decreased fibrosis progression, and decreased HCC incidence (1.2% vs. 2.6%, p<0.01). In multivariable models, statins remained significantly associated with SVR (OR=1.44, 95%CI=1.29,1.61) and progression to cirrhosis (HR=0.56, 95%CI-0.50,0.63) Other factors significantly associated with the development of cirrhosis included SVR attainment, alcohol abuse, diabetes, HCV genotype and viral load, age, and race. Statin use was significantly associated with decreased HCC (HR=0.51, 95% CI=0.34,0.76) when adjusting for baseline fibrosis and controlling for other relevant clinical factors.

Figure. Fibrosis progression by receipt of statin therapy overall (panel A) and by stain therapy and attainment of sustained virologic response (panel B), and time to first diagnosis of cirrhosis by stain therapy (Panel C) and attainment of sustained virologic response (panel D),



Conclusions: In this large, national cohort of persons who initiated anti-HCV treatment, administration of statins in addition to anti-HCV therapy significantly improved SVR, reduced fibrosis progression and reduced incidence of HCC.

644 Sofosubuvir, Simeprevir, +/- Ribavirin in HCV Protease Inhibitor-Experienced Patients

Kristen M. Marks; Ethan M. Weinberg; Sonal Kumar; Carrie Down; Ype P. de Jong; Leah A. Burke; Mary C. Olson; Ira M. Jacobson

Weill Cornell Medical College, New York, NY, US

Background: Little data exists on use of HCV protease inhibitors (PIs) as part of a treatment (Rx) regimen for PI-experienced G1 patients (pts). Since polymorphisms associated with PI-resistance decrease to baseline levels over time in most studied subjects, sofosbuvir (SOF) + simeprevir (SMV) +/- ribavirin (RBV) represents a *potential* retreatment option for PI-experienced pts.

Methods: We compiled a retrospective cohort of HCV PI-experienced G1 pts treated with SOF+SMV+/-RBV at our center. Baseline factors including prior regimen & Rx response, fibrosis stage, HCV genotype & resistance testing (population-based) data, viral RNA levels, demographic data as well as on Rx response, SVR4, and SVR12 were collected and reported.

Results: In 2014, 15 pts with genotype 1 and prior PI experience initiated Rx because of clinical need with 12 wks SOF+SMV with (10) or without (5) RBV . Median age was 61 yrs (range 26-73), baseline HCV RNA 6.5 log IU/ml (5.5-7.0 log), 12 were male, and 10 had cirrhosis. PI Rx occurred 26 (5-85) months prior and included telaprevir (10), boceprevir (3), ABT 450/r (1), GS9451 (1) as part of Rx regimen with 11 nonresponders, 1 relapser, and 3 intolerant of Rx. All had genotype and resistance testing performed prior to SOF+SMV+/-RBV. Of the 9 G1a pts, Q80K was detected in 4, Q80L in1. Of the 6 G1b pts, V36I and T54S were detected in 1 pt each. No other mutations associated with PI resistance were detected.

Responses to SOF+SMV+/-RBV are shown in the table.

	Wk 4 on Rx	End of Rx	Wk 4 post Rx (SVR 4)	Wk 12 post Rx (SVR12)
# completing time point	15	15	14 (1 pending)	13 (2 pending)
# (%) suppressed below quantification (<15 or <43 IU/ml)	15 (100%)	15 (100%)	13 (93%)	12 (92%)
# (%) suppressed below detection	9 (56%)	15 (100%)	13 (93%)	12 (92%)
# relapse (%)			1* (7%)	1* (8%)

*The pt with relapse received SOF+SMV+RBV, had G1b, cirrhosis and a prior history of telaprevir-based Rx completed 14 months prior, and had no known mutations associated with resistance.

Conclusions: Conclusion: SOF+SMV+/-RBV treatment may be appropriate for carefully selected PI-experienced G1 pts including those with cirrhosis. Further study is needed to confirm these findings.

645 Effectiveness of Sofosbuvir/Simeprevir for HIV/HCV Patients in Clinical Practice

Jody Gilmore[1]; Kenneth Lynn[1]; Delisha Breen[1]; Stacey Trooskin[2]; Jihad Slim[3]; Nancy Scangarello[3]; Alvin Kingcade[4]; Katie Hunyh[4]; Vincent Lo Re[1]; **Jay R. Kostman**[1]

[1]Perelman School of Medicine, Philadelphia, PA, US; [2]Drexel University College of Medicine, Philadelphia, PA, US; [3]St Michael's Medical Center, Newark, NJ, US; [4]Philadelphia Health Management Corporation, Philadelphia, PA, US

Background: HIV/HCV-coinfected patients have been underrepresented in clinical trials of all-oral therapies for chronic HCV genotype 1 infection. Our objective was to assess virologic responses and tolerability of sofosbuvir + simeprevir (sof/sim) in HIV/HCV-coinfected patients compared to those with HCV alone.

Methods: We performed a cohort study among HCV-infected patients treated with sof/sim at 4 community-based and academic centers. The main outcome was end-of-treatment (EOT) HCV virologic response. HCV RNA, liver aminotransferases, and sof/sim discontinuations were evaluated over 12 weeks of treatment and 12 weeks of follow-up. Results were stratified by HIV status and by the presence of advanced hepatic fibrosis/cirrhosis.

Results: Eighty-one patients (37 coinfected; 44 monoinfected) were treated with sof/sim between 12/2013 and 9/2014. Fifty-nine percent were African American, 61% were male, 73% had METAVIR stage 3/4 fibrosis, and 46% had prior HCV therapy (49% null or partial responders; 16% relapsers; 35% stopped due to toxicity). The most common HIV regimens in coinfected persons included raltegravir, dolutegravir, or rilpivirine with either tenofovir/emtrictabine or abacavir/lamivudine. Among HIV/HCV patients, 54% and 87% achieved an HCV RNA that was not quantifiable at 2 and 4 weeks of therapy, respectively, compared to 55% and 81% for HCV-monoinfected patients ($p>0.5$). Those with METAVIR stage 3/4 were equally likely to achieve HCV suppression by 4 weeks compared to those with less fibrosis regardless of HIV status (61% vs. 67% in coinfected patients, $p=0.68$; 56% vs. 75% in monoinfected patients, $p=0.33$). Overall, mean levels of alanine aminotransferase decreased from 54 U/L to 22 U/L within 2 weeks of sof/sim initiation. Of the 81 patients, only 5 (6%; 3 coinfected; 2 monoinfected) prematurely discontinued therapy (1 due to nonresponse; 1 for cutaneous reaction; 3 lost to follow-up). Among 42 patients completing 12 weeks of therapy, 37 (88%) achieved an EOT response (89% in coinfected patients; 88% in monoinfected patients, $p>0.5$). At the time of this analysis, 22 patients were followed for at least 4 weeks after the completion of therapy with 2 virologic relapses in monoinfected patients, 1 with METAVIR stage 3/4.

Conclusions: An all-oral sof/sim regimen was effective for patients with chronic HCV genotype 1, regardless of HIV status, previous treatment response, and stage of fibrosis. Adverse events were rare, even in patients with advanced fibrosis/cirrhosis.

646 German Cohort on Sofosbuvir-Based Therapy for HIV/HCV and HCV Infection (GECOSO)

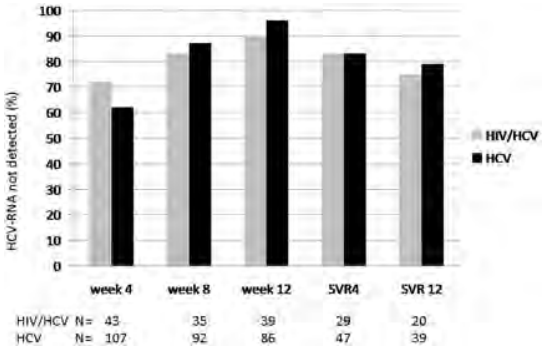
Stefan Christensen[2]; Ingiliz Patrick[3]; Dietrich Hueppe[7]; Thomas Lutz[4]; Karl Georg Simon[6]; Knud Schewe[5]; Heiner Busch[2]; Axel Baumgarten[3]; Guenther Schmutz[1]; **Stefan Mauss**[1]

[1]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; [2]CIM Infectious Diseases, Muenster, Germany; [3]Medizinisches Infektiologie Zentrum Berlin, Berlin, Germany; [4]Infektiologikum, Frankfurt, Germany; [5]Infektionsmedizinisches Centrum Hamburg, Hamburg, Germany; [6]Practice for Gastroenterology Leverkusen, Leverkusen, Germany; [7]Practice for Gastroenterology Herne, Herne, Germany

Background: Sofosbuvir (SOF) was approved in Europe in January 2014 with limited study data. In particular, interferon based triple therapy in HIV/HCV coinfection and pretreated patients were not systematically studied. Here, we present real-life data on SOF-based treatments from Germany.

Methods: In this multicenter cohort, all patients who were started on the following treatment regimens were documented: SOF/ribavirin (RBV), SOF/daclatasvir, SOF/simeprevir, and SOF/PegIFN/RBV. For the current analysis due to the limited observational period only patients treated with PegIFN/RBV/SOF were analysed. In February 2015 complete data sets for the first three therapy regimen will be available.

Results: Overall, 266 patients were enrolled so far. Of those, 193 were HCV-monoinfected and 73 HIV/HCV-coinfected. The genotype (GT) pattern was: GT1 n=156, GT2 n=17, GT3 n=68, GT4 n=24. Liver cirrhosis was present in 85/266 (32%) patients. Pretreated patients were 134/266 (50%). 161 (61%) patients were treated with SOF/PegIFN/RBV. The SVR12 rate overall was 78%.The viral response under therapy did not substantially differ between HIV/HCV coinfection and HCV-monoinfection (see figure). In addition SVR 4 and 12 were comparable. One patient showed a non-response (HCV) and one got re-infected under therapy with a different genotype (HIV/HCV). So far <5% of patients discontinued therapy prematurely or were lost to follow up.



Conclusions: In this preliminary analysis, response rates for HIV/HCV-coinfected and HCV-monoinfected patients treated with SOF/PegIFN/RBV were similar. The SVR12 rate seems to be lower than in the NEUTRINO study despite a low discontinuation rate. The lower SVR rate may be attributable to the cohort population containing more difficult-to-treat patients.

647 Real-World Data on HIV-Positive Patients With HCV Treated With Sofosbuvir and/or Simeprevir

David Del Bello[1]; Kian Bichoupan[1]; Calley Levine[1]; Agnes Cha[2]; David Perlman[1]; Nadim H. Salomon[1]; Donald Kotler[1]; Daniel Fierer[1]; Douglas Dieterich[1]; Andrea Branch[1]

[1]Mount Sinai Health System, New York City, NY, US; [2]Brooklyn Medical Center, New York City, NY, US

Background: We are investigating the effectiveness of simeprevir (SMV) and sofosbuvir (SOF) in a real-world setting for patients with HIV/HCV co-infection.

Methods: Data on 80 HIV/HCV co-infected patients who initiated therapy between 12/2013 and 8/2014 were analyzed. Baseline and week-2 on-treatment data are reported. Week-4 and Week-12 post end-of-treatment responses were examined to determine the sustained virologic response (SVR) rates for patients who have completed therapy. Advanced fibrosis/cirrhosis was defined as a FIB-4 score ≥ 3.25. By 2/2015, SVR4 data will be available for all 80 patients. Data will also be available for additional co-infected patients (enrollment is on-going) and for a comparison cohort of patients with HCV mono-infection.

Results: Median age of the 80 HIV/HCV co-infected patients was 57 yr (range, 25-73 yr), 84% were male, 63% were white, 25% were black, and 38% were Hispanic. Nearly half (41%) were naïve to HCV treatment. Comorbidities were common: 50% had hypertension, 38% had depression, 16% had diabetes, 51% had advanced fibrosis/cirrhosis, and 8% had HCC. The baseline median HCV VL was 6.31 IU/mL (IQR: 5.9-6.7 IU/mL), platelet count was 135 x10^3/μL (IQR: 97-195 x10^3/μL), albumin was 3.9 g/dL (IQR: 3.6-4.2 g/dL), total bilirubin was 0.6 mg/dL (IQR: 0.5-1.0 mg/dL), and the CD4 count of the 54 patients with these data was 487 (IQR: 325-620); HIV VL was undetectable in 46/54 (85%). All but four patients were on HAART. Of 67 patients with genotype (gt) 1, 33 (39%) were on SOF/ribavirin (RBV), 15 (22%) were on SMV/SOF/RBV, and 19 (28%) were on SMV/SOF; 15 (22%) patients changed HAART to accommodate SMV. All 13 patients with gt 2 or 3 HCV were on SOF/RBV. At week-2, 66% of patients had data available. Of 26 gt 1 patients on SMV, HCV RNA was undetectable in 9 (35%). Of 27 patients on SOF/RBV, HCV RNA was undetectable in five (20%). SVR4 data are available for 28 gt 1 patients:15/15 (100%) on a SMV regimen achieved SVR4, as did 7/13 (54%) on SOF/RBV. SVR12 data are available for seven patients on SMV/SOF, all achieved SVR12. Only one gt 1 patient on SOF/RBV achieved SVR12.

Genotype	N (% of total)	Median age, years (Range)	FIB-4 score ≥3.25, n (%)	Naïve, n(%)	SVR4 rate
1 SMV/SOF ± RBV SOF/RBV	67 (84%) 34 (43%) 33 (41%)	57 (25-73) 56 (25-70) 56 (34-73)	36/67 (54%) 19/34 (56%) 17/33 (51%)	26/67 (39%) 16/34 (47%) 10/33 (30%)	22/28 (79%) 15/15 (100%) 7/13 (54%)
2	7 (9%)	60 (46-63)	2/7 (29%)	2/7 (29%)	1/2 (50%)
3	6 (7%)	56 (54-69)	3/6 (50%)	4/6 (66%)	3/4 (75%)

Table. Characteristics and SVR 4 rates stratified by genotype

Conclusions: SMV and SOF are important and highly effective DAAs for HIV/HCV co-infected patients, a group that was notoriously difficult to treat with interferon. SVR4 was achieved by all 15 patients treated with SMV/SOF (with or without RBV) who have reached the 4-week post end of treatment time point (DA031095, DK090317).

648 Simeprevir and Sofosbuvir Regimens for Hepatitis C: Decompensation and Serious AEs

Ponni V. Perumalswami[1]; Kian Bichoupan[1]; Lawrence Ku[1]; Neal M. Patel[1]; Rachana Yalamanchili[1]; Thomas Schiano[1]; Mark Woodward[2]; Douglas Dieterich[1]; Andrea D. Branch[1]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, US; [2]George Institute for Health at the University of Oxford, Oxford, United Kingdom

Background: New therapies for hepatitis C virus (HCV) were well-tolerated in registration trials; however, results in real world clinical practice can be different. We characterized hepatic decompensation and serious adverse events (SAEs) in patients receiving standard care at the Mount Sinai Medical Center.

Methods: All HCV infected patients treated with regimens that contained sofosbuvir (SOF) and/or simeprevir (SMV) were included. The Cases experienced at least one of the following: hepatic decompensation, indicated by new or increased jaundice, ascites, encephalopathy, or sepsis, or another SAE. There were two cohorts: Cohort 1 included 466 patients, Cohort 2 included 43 liver transplant (LT) patients. The incidence of decompensation/SAE was calculated for each cohort. Within each cohort, a matched Case-Control study was performed to identify risk factors for decompensation/SAE. For Cohort 1, up to five Controls were selected for each Case based on treatment regimen and duration. For Cohort 2, matching was 1:2. Cases and Controls were compared using matched conditional exact analysis.

Results: A total of 489 patients met the inclusion criteria: 466 in Cohort 1 (non-LT) and 43 in Cohort 2 (LT). There were 13 non-LT Cases (2.8%) and 8 LT Cases (19%), $p< 0.01$ for the comparison. In Cohort 1, most (62%) were on SOF/RBV, 15% were on SOF/PEG/RBV, and 23% were on SMV/SOF. Among 67 non-LT patients on PEG/RBV-free regimens, three decompensated/experienced an SAE (4%). In Cohort 2, all were on SOF/RBV. Treatment was discontinued in 4/13 (31%) of non-LT Cases and in 2/8 (25%) of LT Cases. Similar to registration trials, liver decompensation/SAE lead to treatment discontinuation in 1% (5/466) of the entire non-LT Cohort and in 5% (2/43) of the entire LT Cohort. Among non-LT patients, risk factors for SAE/decompensation included low baseline albumin, high INR, and high total bilirubin. In LT patients, lower hemoglobin, eGFR, ALT, AFP and higher serum creatinine were risk factors for SAE/decompensation.

Conclusions: This study identified subgroups of non-LT and LT patients who may require more intensive monitoring and additional interventions to successfully complete SMV- and SOF-based treatment regimens. Patients with reduced hepatic biosynthetic function and LT patients were especially vulnerable to serious AEs and decompensation (DA031095, DK090317).

649 Successful HCV Treatment With Direct Acting Antivirals in HIV/HCV Patients

Jennifer L. Grant[1]; Valentina Stosor[1]; Frank J. Palella[1]; Richard M. Green[1]; Guajira Thomas[1]; Donna V. McGregor[1]; Milena M. McLaughlin[2]; Sudhir Penugonda[1]; Michael Angarone[1]; **Claudia Hawkins**[1]

[1]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [2]Midwestern University, Chicago, IL, US

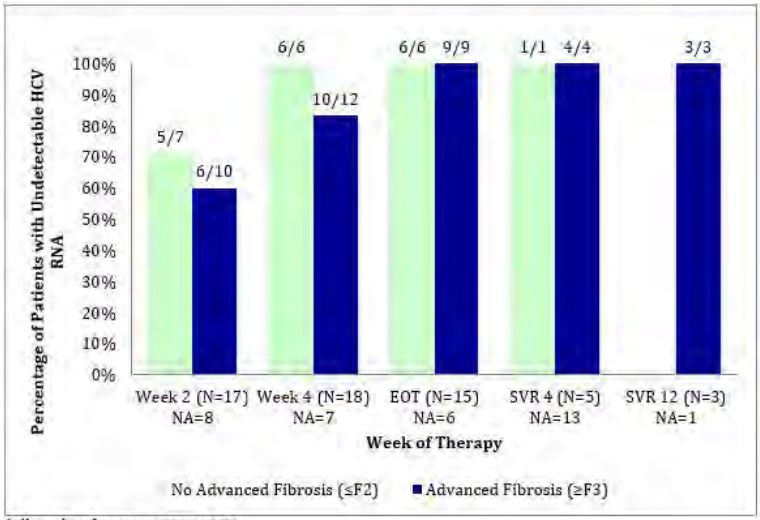
Background: IFN-free combinations of direct acting antivirals (DAA) are associated with high cure rates in HCV-infected patients. The SOF/SMV combination has not yet been studied in HIV/HCV co-infected persons. We evaluated outcomes in HIV/HCV patients receiving IFN-free DAA therapy in a large urban clinic in Chicago.

Methods: In a prospective observational analysis of HCV treatment experienced and treatment naïve co-infected adults (≥18 years) enrolled in the Northwestern University Viral Hepatitis Registry from Jan-Sep 2014, we evaluated the efficacy and safety of SOF/RBV (24 weeks) and SOF/SMV (12 weeks). HCV virologic responses were assessed at week 2 and then monthly during therapy (Rx) and 4 and 12 weeks after completion of Rx (SVR 4 and 12). HCV relapse was defined as a detectable HCV-RNA (lower limit of detection 15 IU/mL) at 4 or 12 weeks after Rx completion. We used chi-square and students' T-test (SPSS version 22.0, Armonk, NY; IBM Corp.) for between group comparisons.

Results: We evaluated 42 HIV/HCV patients [median age 53 years (IQR 47, 60); 81% male; 50% Caucasian; median CD4+ T cell count 522 cells/mm^3 (IQR 292, 660)] for HCV Rx. Risk factors for HCV included MSM (41%) and IDU (41%). Rx was initiated in 32/42 (76%) patients with either SOF/SMV (28, 87.5%) or SOF/RBV (4, 12.5%). Males (85.3% vs. 25% (females); $p<0.01$) and patients with higher mean FibroSure™ scores (0.70 vs. 0.46; $p=0.047$) were more likely to receive HCV Rx. There were 21 (66%) with genotype (GT) 1a, 8 (25%) with GT 1b, and 1 each (3%) with GT 2, 3 and undifferentiated. 14/32 (44%) had previously received either PEG/RBV (12/14) or PEG/RBV+BOC (2/14). Median pre-Rx HCV-RNA was 1,384,532 copies/ml (IQR 798,853, 3,772,827) and 23/32 (72%) had advanced liver fibrosis (≥F3). All patients received indicated ART. HCV-RNA responses are shown in Figure

1. No HCV relapses have occurred to date in patients receiving either DAA Rx. Minor adverse effects occurred in 14/29 (48%) patients, none of which resulted in HCV therapy discontinuation (pruritus, 17%, fatigue, 14%, grade 3 total bilirubin elevation, 10%). One death occurred unrelated to HCV Rx.

Figure 1.
HCV Virologic Outcomes in HIV/HCV Patients Receiving SOF/SMV



*All p-values for comparisons >0.05
**NA=lab data not available

Conclusions: In this non-clinical trial-based study of difficult to treat HIV/HCV-infected patients, use of SOF/SMV or SOF/RBV achieved rapid HCV-RNA declines and was well tolerated. HIV co-infection should not be considered a barrier to successful HCV treatment using these combinations. Accrual and treatment of patients is ongoing.

650 Sofosbuvir/Daclatasvir in HIV/HCV Co-infected Patients With Extensive Liver Fibrosis

Alissa Naqvi; Francine Guillouet de Salvador; Isabelle Perbost; Brigitte Dunais; Aline Joulié; Rodolphe Garraffo; Pascal Pugliese; Jacques Durant; Pierre Marie Roger; Eric Rosenthal
Centre Hospitalier Universitaire de Nice, Nice, France

Background: All-oral combination of sofosbuvir (SOF), a pan genotypic HCV NS5B inhibitor, plus daclatasvir (DCV), NS5A inhibitor, has been poorly evaluated in HIV/HCV co-infected. Interactions between this anti-HCV regimen and antiretroviral drugs (ART) have been poorly investigated. We evaluated the safety and efficacy of SOF plus DCV and plasmatic concentrations of antiviral drugs in HCV/HIV co-infected patients.

Methods: HCV patients with extensive liver fibrosis (METAVIR F3 and F4) and stable HIV disease received SOF 400 mg QD and DCV (30, 60 or 90 mg QD) for 24 weeks. Residual plasma concentrations of DCV, sofosbuvir's metabolite (GS331007) and ongoing ART were determined on patient's blood samples 15 days after starting HCV treatment. The primary efficacy endpoint was sustained virologic response 12 weeks after treatment discontinuation (SVR12).

Results: Baseline characteristics of the 26 patients are shown in the table. HCV viral load under treatment was undetectable in 4/19 (21%) at Day (D)15, 7/14 (50%) at Week (W) 4, 11/12 (92%) at W8, 8/8 (100%) at W12 and 4/4 (100%) at W16. SVR12 results and pharmacological testing will be presented. During the first weeks of treatment, DCV plus SOF combination therapy was well tolerated with no grade 4 adverse events or drug discontinuation.

Baseline characteristics of patients, n = 26

Male, n (%)		20 (77)
Undetectable HIV load at D0, n (%)		25 (96)
CD4 T-cell count (cells/microL), mean (SD)		559 (299)
Liver fibrosis score, n (%)	F3 F4	5 (19) 21 (81)
Log10 HCV RNA (IU/ml), mean (SD)		5.8 (1.0)
HCV genotype, n (%)	1a 1b 3a 4	16 (62) 5 (19) 3 (12) 2 (8)
Patients on ART, n (%)	2 NRTIs* + 1 NNRTI** 2 NRTIs + PI/r*** 2 NRTIs + 1 INSTI**** Other combinations	4 (15) 2 (8) 9 (35) 11 (42)
Prior HCV treatment, n (%)	Naïve Interferon + Ribavirin Interferon + Ribavirin + Telaprevir	4 (15) 17 (65) 3 (12)
Prior HCV treatment response, n = 22 (%)	Non-response Relapse Premature treatment discontinuation for AE Failure poorly characterized	10 (45) 2 (9) 7 (32) 3 (14)
SVR4		1/1
SVR12		[To be presented]
Pharmacological testing		[To be presented]

*NRTI, Nucleoside Reverse Transcriptase Inhibitor; **NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor; ***PI/r, Protease Inhibitor/ritonavir boost; ****INSTI, Integrase Strand Transfer Inhibitor

Conclusions: Interferon-free treatments for HCV are needed for HIV/HCV co-infected patients. Pharmacological testing of DCV and SOF is needed to assess drug interactions with HIV antiviral therapy. The preliminary data suggest that DCV plus SOF treatment is well-tolerated and safely co-administered with multiple ART regimens to patients with extensive liver fibrosis.

651 Majority of HIV/HCV Patients Need to Switch ART to Accommodate Simeprevir

Rebecca Cope[1]; Aaron Pickering[2]; Thomas Glowa[1]; Samantha Faulds[1]; Peter Veldkamp[1]; **Ramakrishna Prasad**[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]University of Maryland, Glen Burnie, MD, US

Background: The impact of drug-drug interactions (DDIs) between Simeprevir (SMV) and antiretrovirals (ART) in limiting HCV treatment among HIV/HCV co-infected individuals in clinical practice settings is unknown. We determined: a) the need to switch antiretroviral therapy (ART) prior to initiation of SMV; and b) the feasibility of switching ART to allow SMV use. We hypothesized that the majority of co-infected patients will require an ART switch and a safe and effective ART switch will be challenging in patients on a protease inhibitor (PI) based ART regimen.

Methods: A retrospective chart review was conducted at the University of Pittsburgh Medical Center's HIV/AIDS Program from June-August 2014. All patients with HIV and chronic HCV with a visit in the past 18 months were included. After collection of baseline characteristics, significant interactions between SMV and ART were identified based on available literature. If DDIs limited use of SMV, previous HIV genotype reports were reviewed to determine the feasibility of a safe and effective ART switch.

Results: Of 133 patients, 71% were male, 54% African American, 23% met criteria for advanced liver disease, 86% had HCV genotype 1, and 94% were currently on ART. The distribution of regimens was: ritonavir-boosted PI (PI/r) (38%); efavirenz (34%); raltegravir (11%); rilpivirine (6%); elvitegravir/cobicistat (1%); and other regimens including dolutegravir (4%). An ART switch to allow use of SMV was required in 103 (77%), most frequently for patients on efavirenz or a PI/r. For 47 (46%), a straightforward substitution could be made. For the remaining patients, a switch following HIV expert opinion was viable in 40 (39%), but no switch was possible in 16 (15%) due to archived HIV drug resistance mutations. Notably, for more than 30% of patients on a PI, an ART switch was not feasible.

Conclusions: The majority of HIV/HCV co-infected patients will require ART switch prior to use of SMV. Additionally, for nearly a third of patients on a PI, an ART switch may not be feasible. These findings are significant to real world clinical practice settings and highlight the complexity of using Interferon-free DAAs in this population and add further stress to an already burdened HIV care delivery system.

TUESDAY, FEBRUARY 24, 2015

Session P-N3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Treatment of HCV with DAAs: Short-Term Costs and Long-Term Benefits

652 Simeprevir/Sofosbuvir vs Triple Therapy (Telaprevir or Boceprevir) for HCV GT1: A cost analysis

Jacob A. Langness[1]; David Tabano[2]; Sarah Tise[3]; Lindsay Pratt[3]; Lauren Ayres[3]; Amanda Wieland[3]; Sonia Lin[1]; Vahram Ghuschcyan[2]; Kavita Nair[2]; Greg Everson[3]

[1]University of Colorado, Arvada, CO, US; [2]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Aurora, CO, US; [3]University of Colorado, Aurora, CO, US

Background: Simeprevir plus sofosbuvir (with or without ribavirin) (SMV/SOF) increases rates of sustained virologic response (SVR) over telaprevir- or boceprevir-based triple therapy (TT) (89-100% vs 64- 75%). Our objective was to examine the total treatment cost and cost per SVR of SMV/SOF versus TT.

Methods: Patients were included if they had chronic hepatitis C, were infected with HCV genotype 1, and had been prescribed either SMV/SOF or TT between May 1, 2011 - August 1, 2014. Transplant recipients and HIV co-infected patients were excluded. Electronic medical records were used to collect data on: demographics, duration of HCV treatment, virologic response, clinic visits for treatment monitoring, HCV-related emergency room visits, and hospitalizations, treatment related blood transfusions, management of hematologic side effects by medications (epoetin alfa, filgrastim) and outpatient laboratory monitoring (estimated per clinic-defined treatment protocol). Unit costs for all medical services and labs were obtained from a national claims database IMS Lifelink with 8 million covered lives. HCV drug treatment costs were obtained from RED Book. SVR rates were defined by undetectable HCV RNA at 12 weeks (SVR12) for TT and at 4 weeks (SVR4) for SMV/SOF after end of treatment. Cost per SVR was calculated by dividing the mean total cost by the SVR rate.

Results: There were 118 patients in the TT group (mean age = 53) vs 39 patients (mean age = 59) in the SMV/SOF group. Majority were male (54% in TT vs 59% in SMV/SOF) and Caucasian (86% in TT vs 94% in SMV/SOF). The SMV/SOF group had more advanced fibrosis (72% vs 57%), more treatment-experienced patients (64% vs 54%), and improved tolerability than TT. More TT patients (44% vs 0%) discontinued therapy for toxicity or virologic failure. An SVR4 rate of 87% was achieved in the SMV/SOF vs an SVR12 rate of 62% in the TT group. The cost per SVR4 in SMV/SOF group was $187,365 vs cost per SVR12 of $150,584 in the TT group. Majority of the costs in both groups were HCV drug costs, however HCV-related medical costs (outpatient, emergency room, and inpatient visits, laboratory monitoring, and hematologic side effect management) were 6 times higher in the TT group ($12,962 per patient) vs SMV/SOF ($2,279 per patient) (Table 1).

Table 1: Cost Analysis

Mean cost per patient	SMV/SOF +/- ribavirin	Triple Therapy
n	39	118
Direct Medical Costs		
Cost for HCV Medications	$ 161,064	$ 80,196
EPO and filgrastim Costs	$ 0	$ 3,029
Lab Monitoring Costs	$ 1,033	$ 1,497
Medical Costs (clinic visits, hospitalizations and emergency room visits)	$ 1,246	$ 8,436
Total Mean Costs per Patient	$ 163,344	$ 93,158
SVR rate	87% (SVR4)	62% (SVR12)
Cost per SVR	$ 187,365	$150,584

Conclusions: This interim analysis shows SMV/SOF has more favorable efficacy and tolerability especially in more difficult-to-treat patients with HCV genotype 1 infection, but is associated with higher medication costs and cost per SVR.

653 SVR Durability: HCV Patients Treated With IFN-Free DAA Regimens

Aurielle M. Thomas[1]; Sarah Kattakuzhy[1]; Sarah Jones[2]; Anita Kohli[1]; Wilson Eleanor[2]; Angie Price[2]; Rachel Silk[2]; Zayani Sims[1]; Anu Osinusi[3]; Shyam Kottilil[3]

[1]The National Institutes of Health, Bethesda, MD, US; [2]Leidos Biomedical Research, Inc., Bethesda, MD, US; [3]Institute of Human Virology, University of Maryland, Baltimore, MD, US

Background: IFN-based treatment of chronic hepatitis C has demonstrated a late relapse rate of <5%, usually occurring within 2 years of treatment. While high rates of SVR12 weeks after completion of directly-acting antiviral combinations has been established, data on long-term durability of SVR achieved through IFN-free regimens are lacking. The objective of this analysis was to analyze data from multiple studies utilizing IFN-free DAA-based regimens to define the durability of SVR and evaluate for associated changes in biomarkers related to liver and metabolic fitness.

Methods: Data on patients who achieved SVR12 from the following clinical trials were included: SPARE (HCV monoinfected, SOF+ RBV x 24 wks, n=38); SYNERGY (HCV monoinfected, SOF/LDV x 12 wks, n=20, SOF/LDV + GS-9669 X 6 weeks, n=19, SOF/LDV + GS-9451 X 6 weeks n=19) and ERADICATE (HIV/HCV coinfected, SOF/LDV X 12 weeks, n=49). HCV viral loads and serum biomarkers were collected up to SVR108. HCV viral loads were measured with Abbott M2000 RealTime HCV assay, with a limit of quantification of <12 IU/mL.

Results: Of 138 patients followed for a period ranging from 1 to 96 weeks (averaging 35 weeks) post SVR12, 138 patients (100%) maintained HCV viral loads at <12 IU/mL (Table 1) with no current evidence of late relapse. At SVR12 timepoint, 86% of patients had ALT within normal range. At the current furthest timepoint, averaging 35 weeks after SVR12, 91% of patients had ALT within normal range.

WEEKS POST SVR12 (WEEKS)		0	12	24	36	48	60	72	84	88	96
SVR (WEEKS)		SVR12	SVR24	SVR36	SVR48	SVR60	SVR72	SVR84	SVR96	SVR100	SVR108
	HCV VL<12/N	138/138	112/112	84/84	36/36	27/27	26/26	25/25	11/11	3/3	1/1
	% SVR	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

Durability of Sustained Virologic Response

Conclusions: This study shows the long-term durability of SVR associated with DAA-based therapy during ongoing assessment of up to 2 years. While the rise in percentage of ALT within normal range over the average follow up period was minimal, it may suggest an association with SVR durability. It is plausible that this change reflects the long-term histologic regression of necroinflammation and fibrosis described in patients who achieve SVR. Ongoing data collection including liver biopsy and radiologic studies are underway to continue analysis of this novel population.

654 Five–Year Risk of Late Relapse or Reinfection With Hepatitis C After Sustained Virological Response: Meta-analysis of 49 Studies in 8534 Patients

Andrew M. Hill[1]; Bryony Simmons[2]; Jawaad Saleem[2]; Graham Cooke[2]

[1]Chelsea and Westminster Hospital, London, United Kingdom; [2]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom

Background: Combination treatment with direct acting antivirals can lead to sustained virological response (SVR) in over 90% of people with Hepatitis C (HCV) infection. However, subsequent recurrence of HCV (either from late relapse or re-infection) reverses the beneficial effects of SVR. This analysis aimed to estimate the 5-year risk of HCV late relapse or re-infection post-SVR, by risk group.

Methods: The MEDLINE and EMBASE databases were searched for studies analysing late relapse or re-infection post-SVR (typically 24 weeks post-treatment, using pegylated interferon/ribavirin). All studies with >6 months of follow up post-SVR were included. Three groups of patients were analysed: 1. Mono-HCV infected "low risk" patients; 2. Mono-HCV infected "high risk" patients (IV drug users or prisoners); 3. HIV/HCV co-infected patients. Studies of liver transplant patients were excluded. Recurrence was defined as confirmed HCV RNA detectability after SVR (at least 6 months after end of treatment).

Results: Results were available from 49 studies in 8534 patients. In each risk group, there were progressive rises in the risk of HCV recurrence with longer follow up time. In the 24 studies of HCV mono-infected "low risk" patients (n=6046) there were 45 HCV recurrences during a mean 4.1 years of follow up (estimated 5 year rate=0.9%). For the 15 studies of HCV mono-infected "high risk" patients (n=1203) there were 102 HCV recurrences during a mean 5.0 years of follow up (estimated 5-year rate=8.1%). For the 10 studies of HIV/HCV co-infected patients (n=1285) there were 178 HCV recurrences during a mean 3.3 year follow up (estimated 5-year rate=21.8%). For the studies of HIV/HCV co-infected patients, 5-year rates of HCV recurrence were significantly lower for patients followed up after randomised clinical trials (1.25%), compared to unselected patient cohorts (24.0%) (p<0.001).

Risk Group	Mono-infection, low-risk	Mono-infection high risk	HIV/HCV co-infected
Number of patients	6046	1203	1285
Mean Follow up (years)	4.1	5.0	3.3
5-year re-infection risk (%)	0.9%	8.1%	21.8%

5-year HCV re-infection rates by risk group

Conclusions: In this analysis of 49 studies, the 5-year risk of late relapse or re-infection post-SVR was 0.9% in HCV mono-infected "low risk" patients, 8.1% in HCV mono-infected IV drug users or prisoners, and 21.8% in HIV/HCV co-infected patients. The large differences in event rates by risk group suggest that re-infection is more significantly more common than late relapse. Studies which follow up HIV/HCV co-infected patients originally enrolled in clinical trials may underestimate the risk of HCV re-infection in the general population

655 Incidence of Extrahepatic Complications in HIV/HCV Patients Who Achieved SVR

Sebastiano Leone[1]; Mattia Prosperi[2]; Silvia Costarelli[1]; Francesco Castelli[3]; Franco Maggiolo[4]; Simona Di Giambenedetto[5]; Annalisa Saracino[6]; Massimo Di Pietro[7]; Fabio Zacchi[8]; Andrea Gori[1]

[1]"San Gerardo Hospital", University of Milano-Bicocca, Monza, Italy; [2]University of Manchester, Manchester, United Kingdom; [3]University of Brescia, Brescia, Italy; [4]Ospedali Riuniti, Bergamo, Italy; [5]Policlinico Gemelli, Rome, Italy; [6]Policlinico of Bari, Bari, Italy; [7]S.M Annunziata Hospital, Firenze, Italy; [8]Istituti Ospeitalieri di Cremona, Cremona, Italy

Background: There is increasing evidence that the achievement of sustained virologic response (SVR) after interferon plus ribavirin treatment reduces the incidence of liver-related events. Data on the effects of SVR on the outcome of extrahepatic complications are scarce. Therefore, we conducted this study to assess the impact of SVR on the incidence of chronic kidney disease (CKD), diabetes mellitus (DM), and cardiovascular disease (CVD) in a cohort of HIV/HCV patients.

Methods: We analyzed all coinfected HIV/HCV patients in the MASTER cohort in order to estimate the incidence of CKD, DM and CVD. Patients were divided into 2 groups: SVR and non-SVR (naïve or non-responder to anti-HCV treatment). CKD and DM were defined as eGFR and fasting glucose plasma levels <60 mL/min/1.73 m^2 and >126 mg/dL in 2 consecutive time points, respectively. All major CVD, including coronary heart disease, cerebrovascular disease, chronic heart failure and peripheral vascular disease were evaluated. Cirrhosis was defined by a FIB-4 score >3.25. Kaplan-Meier curves and Cox regression analyses were used.

Results: Data of 5407 patients were analysed (75.86% male, 64.79% IVDU, GT1 28.37%, cirrhosis 12.21%). Overall, the incidence of CKD, DM, CVD and death were 3.97 (95% confidence interval [CI]:3.46-4.53), 8.09 (95%CI:7.34-8.90), 4.32 (95%CI:3.79-4.91), 8.24 (95%CI:7.50-9.04) per 1000 person years of follow-up (PYFU). In the Cox regression analysis, SVR was not associated with a lower risk of CKD (relative hazard [RH]:1.16;95%CI:0.8-1.69), DM (RH 0.96;95%CI:0.71-1.29), CVD (RH 0.88;95%CI:0.58-1.32) and death (RH 0.98;95%CI:0.76-1.28) compared to non-SVR group. Moreover, no differences were observed in patients who received more cycles of anti-HCV treatment. Cirrhosis was significantly associated with the risk of CKD (RH 1.62;95%CI:1.15-2.28), DM (RH 2.66;95%CI:2.12-3.34), CVD (RH 1.5;95%CI:1.06-2.12) and death (RH 5.5;95%:4.45-6.8).

Conclusions: Our results suggest that the achievement of an SVR after anti-HCV treatment in patients coinfected with HIV/HCV does not reduce liver-related extrahepatic complications and mortality. However, people with cirrhosis have an increased risk of CKD, DM, CVD and death. Thus, coinfected patients should early be treated to prevent the progression of liver fibrosis.

656 Impact of SVR on Liver Decompensation and Hepatic Fibrosis Markers in HIV/HCV

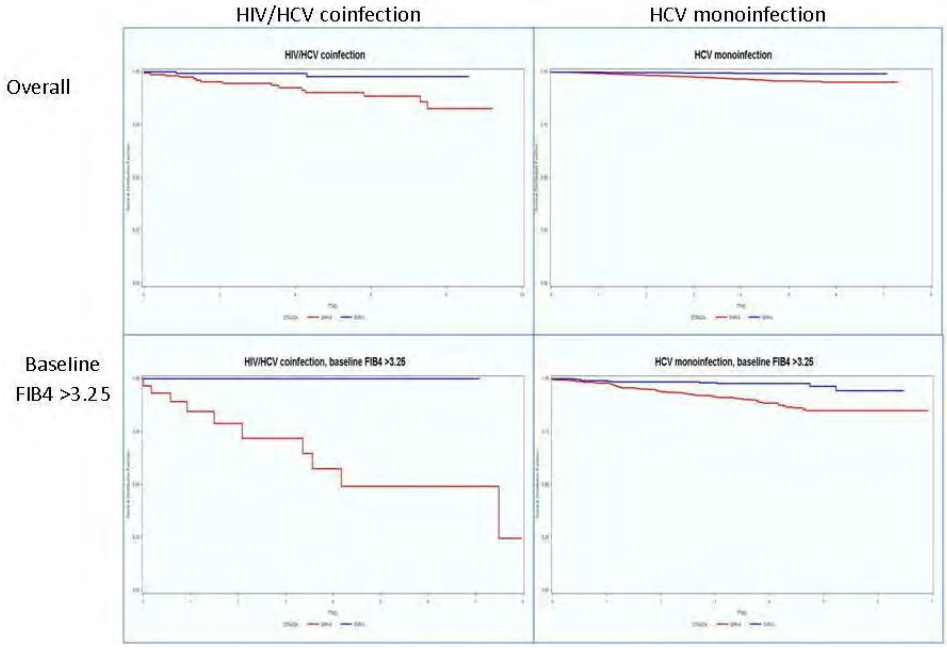
Janet Tate[1]; E. John Wherry[2]; Jay R. Kostman[2]; Debika Bhattacharya[4]; Guadalupe Garcia-Tsao[5]; Cynthia Gibert[6]; Joseph K. Lim[5]; David Rimland[3]; Amy Justice[1]; **Vincent Lo Re**[2]
Veterans Aging Cohort Study Project Team

[1]VA Connecticute Health System, West Haven, CT, US; [2]Univeristy of Pennsylvania, Philadelphia, PA, US; [3]Atlanta VA Healthcare System, Atlanta, GA, US; [4]VA Greater Los Angeles, Los Angeles, CA, US; [5]Yale University School of Medicine, New Haven, CT, US; [6]Washington DC VA Medical Center, Washington, DC, US

Background: It remains unclear if rates of hepatic decompensation (HD) and changes in liver fibrosis differ between HIV/hepatitis C virus (HCV)-coinfected and HCV-monoinfected patients after sustained virologic response (SVR) to HCV therapy. We evaluated the risk of HD and changes in liver fibrosis after SVR in HCV-treated coinfected and monoinfected patients.

Methods: We performed a cohort study of HCV genotype 1, 2, and 3 patients (393 antiretroviral-treated coinfected; 12,598 monoinfected) prescribed pegylated interferon and ribavirin between 2002 and 2011 in the national Veterans Affairs health system. SVR was defined as persistently undetectable HCV RNA beginning 12 weeks after treatment end date. HD was defined by ascites, spontaneous bacterial peritonitis, and variceal bleed diagnoses. FIB4, a non-invasive measure of hepatic fibrosis, was calculated from 1 year before start of treatment (baseline) through end of follow-up. We used proportional hazards models to estimate the hazard ratio (HR) of incident HD associated with SVR, by HIV and advanced fibrosis/cirrhosis status (FIB4 >3.25). Generalized estimating equation models estimated change in FIB4 by time, SVR, and HIV status.

Results: SVR was associated with a reduced rate of HD in coinfected (3.3 vs. 21.3/1000 pyears; HR, 0.16 [95% CI 0.04-0.70]) and monoinfected (1.4 vs. 8.1/1000 pyears; HR, 0.17; 95% CI, 0.11-0.27]) patients (Figure). Among those with pre-HCV therapy advanced fibrosis/cirrhosis, the risk of HD associated with SVR remained lower for both coinfected (0 vs. 135/1000 pyears) and monoinfected (7.4 vs. 29.4/1000 pyears; HR, 0.25; 95% CI, 0.13-0.47) patients. After SVR, mean FIB4 results were significantly lower and mean platelet counts significantly higher in both coinfected and monoinfected patients.



Conclusions: SVR was associated with a similarly reduced risk of HD in coinfected as in monoinfected patients. After SVR, FIB4 decreased and platelet increases, regardless of HIV status. Future studies should evaluate changes in hepatic fibrosis after SVR with interferon-free direct-acting antiviral-based therapies in both HIV/HCV-coinfected and HCV-monoinfected patients.

657 Portal Pressure Changes After HCV Eradication in HIV/HCV+ Patients With Cirrhosis

Matilde Sánchez-Conde; Leire Pérez-Latorre; Diego Rincón; Pilar Miralles; María Vega Catalina; Juan Carlos López; Rafael Bañares; **Juan Berenguer**

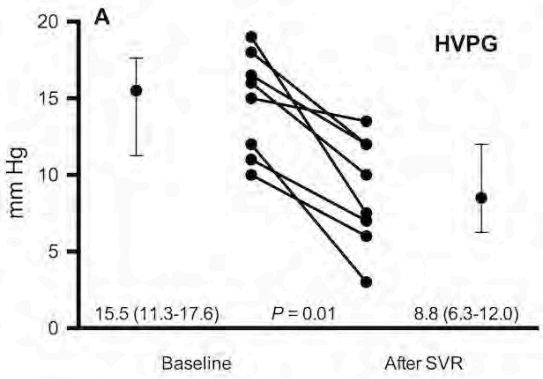
Hospital General Universitario Gregorio Marañón, Madrid, Spain

Background: In patients with compensated cirrhosis (CR), hepatic venous pressure gradient (HVPG) is the most accurate predictor of liver-related events (LRE). In cirrhotic patients receiving pharmacologic treatment for prevention of variceal rebleeding, a decrease in HVPG ≥ 20% or to ≤ 12 mm Hg is associated with a marked reduction in the long-term risk

of developing LRE and with improved survival (*Hepatology 2003;37:902-908*). We assessed the effect of sustained viral response (SVR) after pegylated interferon plus ribavirin (PR) on HVPG in HIV/HCV+ patients with CR.

Methods: We reviewed the records of the portal hemodynamic laboratory of our institution to identify all HIV/HCV+ patients with CR who had a determination of HVPG before and after PR therapy between 2007 and 2012.

Results: HVPG was determined in 60 HIV/HCV+ patients with CR. A total of 27/60 patients were treated with PR, and 15/27 treated patients achieved SVR. Consent to perform a 2nd HVPG determination was given by 8/15 patients with SVR. In these 8 patients, the 2nd HVPG determination was performed a median time of 18 (10 – 26) months after the discontinuation of PR. The median (IQR) HVPG was 15.5 (11.3-17.6) mmHg at baseline, and 8.8 (6.3-12.00) mmHg following SVR; P=0.01. After SVR, 7/8 patients experienced a decrease in HVPG ≥ 20% and all 7 had HVPG ≤ 12 mm Hg. In one patient with SVR, HVPG decreased 10% with a last value of 13.3 mmHg. After a median follow-up time of 60 months, all 8 patients were alive and free from LRE. **Figure 1** shows median and IQR values and individual values of HVPG at baseline and after SVR.



Median and interquartile range (IQR) values, and individual values of hepatic venous pressure gradient (HVPG) at baseline and after sustained viral response (SVR).

Conclusions: Our results suggest that eradication of HCV is associated with a marked and clinically significant reduction of HVPG in most HIV/HCV+ patients with CR and PH. However, some patients with CR and portal hypertension may remain at risk for LRE despite eradication of HCV.

TUESDAY, FEBRUARY 24, 2015

Session P-N4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HCV: Getting the Drugs to Those Who Need Them

658 Assessment of PCP Knowledge of HCV Screening, Recommendations, and Treatment Options

Allison Brodsky; Monique Allen; Gregory Johnson; Lora Magaldi; Carolyn Moy; Nancy Tursi; Stephanie Tzarnas; Stacey Trooskin

Drexel University College of Medicine, Philadelphia, PA, US

Background: According to the CDC 50-75% of those chronically infected with HCV are unaware of their infection. Moreover, adults born between 1945-1965 have rates of HCV five times higher than other adults. CDC guidelines recommend that all baby-boomers be tested for HCV at least once in their lifetime. We aimed to assess primary care provider (PCP) knowledge of HCV screening guidelines and treatment options. We also assessed the accuracy of self-reported testing practices.

Methods: A baseline survey to assess PCP and support staff knowledge about HCV testing, treatment, and guidelines was developed. Only practice-level identifiers were used, the survey was blinded with respect to individual identity. We administered the survey to PCPs at seven primary care practices in the Drexel Medicine network, including MDs and DOs, and to support staff including medical assistants and RNs. Self-reported testing practices were then compared to practice-level testing data extracted from the electronic medical record (EMR).

Results: We surveyed 57 PCPs and 42 support staff**.** Thirty percent of PCPs and 11.9% of support staff surveyed knew that cure rates of HCV are >70% for patients who undergo treatment. Almost 40% of PCPs and 21% of support staff surveyed were aware that HCV can now be cured in 12-24 weeks. Sixty-eight percent of the PCPs, surveyed during May and June 2014, knew the CDC guidelines for birth cohort testing. In May, 6.9% of the 1658 baby-boomers seen in the primary care practices were screened for HCV. In June, 11.5% of the 1609 baby-boomers seen were screened for HCV.

Conclusions: Less than half of the PCPs and support staff surveyed could accurately identify cure rates or treatment duration for HCV, indicating a lack of awareness of recent developments in HCV treatment options. Providers are aware of testing guidelines for baby-boomers, but are not routinely implementing them in their practice. Targeted education to PCPs and support staff regarding new HCV therapies should be provided. Education, however, may not be the only solution; additional tools to assist practices in integrating CDC testing recommendations into clinical workflow are needed. These may include prompts in the electronic medical record and involvement of support staff in the implementation of standardized testing/order placement protocols.

659 Majority of HCV/HIV-Infected Patients in the Netherlands Remain in Need of Effective HCV Treatment

Colette Smit[1]; Joop E. Arends[2]; Marc van der Valk[3]; Kees Brinkman[4]; Heidi Ammerlaan[5]; S. Arend[6]; Peter Reiss[1]; Clemens Richter[7]

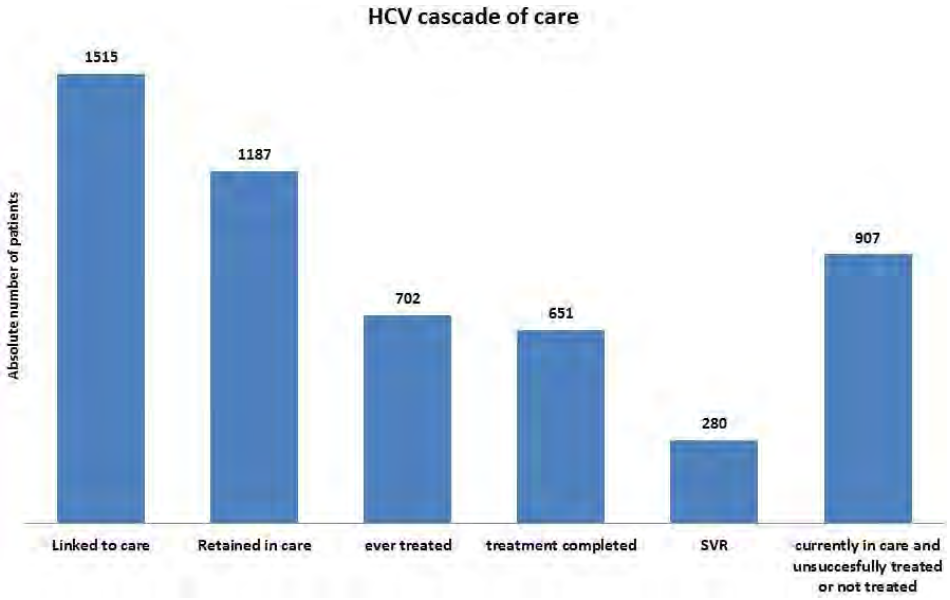
[1]*Stichting HIV Monitoring, Amsterdam, Netherlands;* [2]*Universitair Medisch Centrum Utrecht, Utrecht, Netherlands;* [3]*Academic Medical Center, Amsterdam, Netherlands;* [4]*Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands;* [5]*CZE, Eindhoven, Netherlands;* [6]*Leiden University Medical Center, Leiden, Netherlands;* [7]*Rijnstate Ziekenhuis, Arnhem, Netherlands*

Background: A sustained virologic response (SVR) to HCV treatment is an important step in achieving optimal healthcare outcomes in HCV/HIV co-infected patients. To achieve a SVR, patients must be diagnosed with HCV, engaged in care, and prescribed treatment. The objective of this analysis is to describe the stages of the HCV cascade of care, including

HCV treatment rates in HCV/HIV co-infected patients in active care in the Netherlands. The ATHENA observational cohort captures data from each patient with HIV linked to care in one of the designated Dutch HIV treatment centres, and thereby allows a comprehensive nationwide analysis.

Methods: All HIV-infected patients seen in a HIV treatment centre are registered and monitored by the HIV Monitoring Foundation. We included data from all HIV/HCV co-infected patients who were linked to care between 1998 and 2014, excluding those with documented spontaneous HCV clearance. Patients were considered retained in care if they were alive and in care as of June 2014. HCV treatment included a combination of (pegylated) interferon alfa ((PEG)-IFN) with weight based ribavirin (RBV) or triple therapy of PEG-IFN+RBV with boceprevir or telaprevir. SVR was defined as a negative HCV RNA test result 24 weeks after treatment completion.

Results: Out of a total of 1,515 patients linked to HIV care and diagnosed with HCV, 1,187(78%) patients were retained in care as of June 1, 2014. Of these 1,187 patients, 702(59%) had received treatment for HCV, and 651 of those had completed treatment and were in care for at least 24 weeks after the end of treatment with data available to calculate a SVR rate. SVR was achieved in 280 of these 651(43%) patients. Thus, of the 1,187 HCV/HIV co-infected patients who receive ongoing care in one of the Dutch HIV treatment centres, a total of 907(76%) remain in need of effective HCV therapy, 485 of whom are HCV treatment-naïeve and 422 not successfully treated.



Conclusions: Three quarter of all HCV/HIV-co-infected patients currently engaged in HIV care in the Netherlands remain in need of an effective curative treatment for HCV, of whom approximately equal proportions are HCV treatment-naïeve or -experienced. These data provide important information for estimating the need for highly effective all oral combination regimens of direct acting antivirals, access to which may not only prevent long-term hepatic complications, including hepatocellular carcinoma, but may also impact on the further spread of HCV.

660 Identifying and Prioritizing Hepatitis C Treatment for HIV-Hepatitis C Co-Infection

Amanda D. Castel[1]; Mariah M. Kalmin[1]; Rachel Hart[2]; Alan Greenberg[1]; Henry Masur[3]
DC Cohort Executive Committee

[1]The Milken Institute School of Public Health at George Washington University, Washington, DC, US; [2]Cerner Corporation, Kansas City, MO, US; [3]National Institutes of Health (NIH), Bethesda, MD, US

Background: Current guidelines for HCV management recommend that most patients should be treated. However, the drug cost for directly acting agents is substantial and the number of experienced healthcare providers in the U.S. is insufficient to treat all patients immediately. Thus, the guidelines suggest prioritization of treatment based on host factors including co-infections and degree of liver fibrosis. This analysis describes the prevalence and incidence of HCV, and risk factors for disease progression and transmission in incident HCV cases among a large urban cohort of HIV+ patients.

Methods: Data from persons enrolled in the DC Cohort, a longitudinal observational cohort of HIV+ persons in care in Washington, DC were analyzed. Incident cases were defined based on ICD-9 codes indicative of HCV infection during study follow-up and considered to be a surrogate for active disease among this HIV-HCV co-infected population. Among participants with incident HCV diagnoses since enrollment, demographics, risk factors for HCV progression and transmission including co-morbid conditions, and relevant labs and treatments were collected. Fibrosis-4 (Fib-4) scores were calculated for untreated HCV infected persons. Descriptive analyses were conducted to describe risk factors for HCV transmission and disease morbidity.

Results: Among 6,207 DC Cohort participants, 712 (12%) had a prior diagnosis of HCV documented at study enrollment. The 5,495 participants without HCV at study enrollment had a mean follow-up time of 27.2 months during which 213 (4%) incident cases of HCV were diagnosed. Only 7% of co-infected participants had received treatment for HCV; 64% received non-interferon based regimens. Among untreated participants, most had a high risk of HCV transmission: 27% were infected with HIV through MSM, 25% through IDU, and 2% through MSM/IDU. Among 199 co-infected untreated participants, in addition to HIV, 33% had multiple risk factors for HCV morbidity including Fib-4 scores >3.25 (17%), diagnoses of chronic liver disease/cirrhosis (9%), and hepatitis B infection (5%) (Table).

Table. Demographics and Risk Factors of Persons with HIV and Untreated Chronic HCV Co-infection (N=199)	
Demographics	**No. (%)**
Age (median, IQR)	56.0 (50.7, 60.4)
Sex (male)	147 (73.9)
Race (black)	168 (84.4)
Select High-Risk Complications	
Chronic liver disease and cirrhosis	18 (9.0)
Advanced fibrosis of liver (FIB-4 score >3.25)	31 (16.7)
Kidney disease	16 (8.0)
Hepatitis B co-infection	10 (5.0)
Participants who meet any high-risk criteria*	65 (32.7)
High-Risk of Transmission (MSM, IDU or MSM-IDU)	106 (53.3)

*According to the HCV treatment guidelines, these include insulin resistant diabetes mellitus, kidney disease, proteinuria, nephrotic syndrome, membranoproliferative glomerulonephritis, and all conditions listed above.

Conclusions: In this cohort of HIV+ persons, we found a high proportion of patients had HCV infection at baseline with many new diagnoses identified over a two-year period. While all HIV-HCV co-infected persons are a high priority for treatment, one-third of participants had multiple risk factors for HCV progression. Thus, HCV treatment efforts will present a substantial financial and workforce challenge to the healthcare community.

661 One-Year Results of a Community-Based Hepatitis C Testing and Linkage-to-Care Program

Christian B. Ramers[1]; Robert Lewis[1]; Letty Reyes[1]; Danelle Wallace[1]; Robert Gish[3]; David Wyles[2]; Alex Kuo[1]

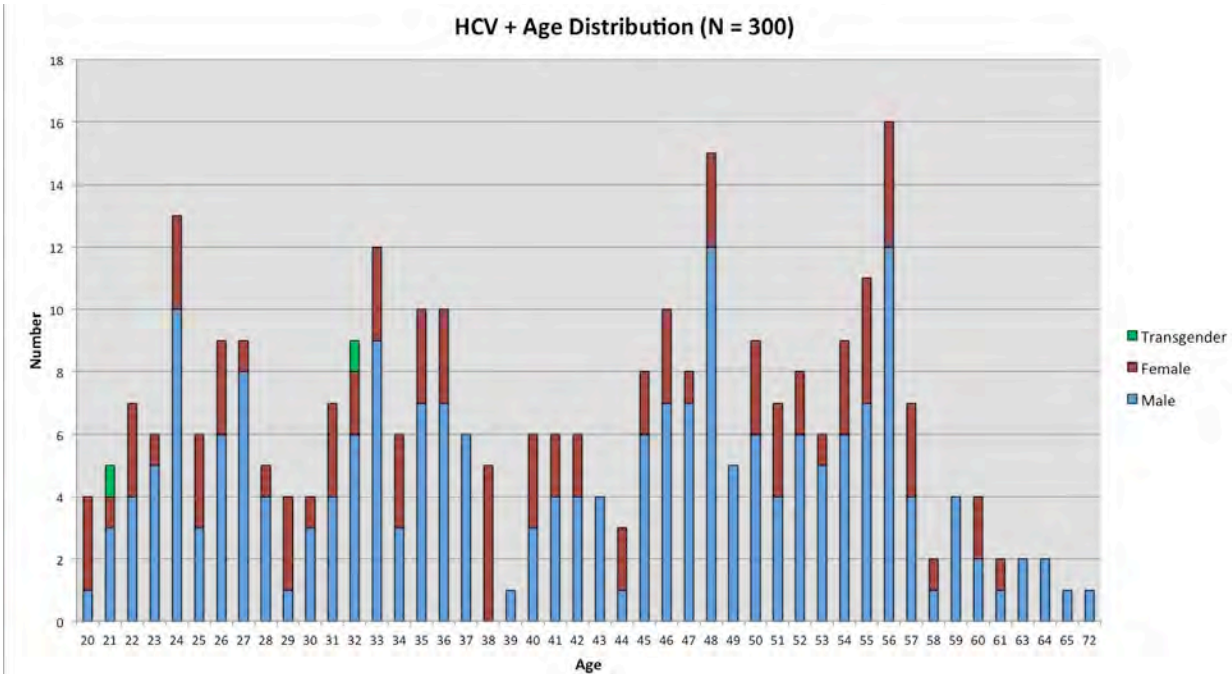
[1]Family Health Centers of San Diego, San Diego, CA, US; [2]University of California San Diego, La Jolla, CA, US; [3]Stanford University, Palo Alto, CA, US

Background: Chronic Hepatitis C virus (HCV) is a major public health concern and the leading chronic viral cause of death in the United States. Less than 1/3 with HCV are aware of their infection. Community-based testing strategies are needed, and uncertainty exists surrounding the implementation of HCV testing, linkage to care, and treatment.

Methods: We conducted a rapid testing and linkage to care program at urban community health centers and alcohol and drug treatment programs. HIV test counselors were trained on HCV testing methods. Demographic, risk-factor, and clinical data were collected prospectively. Rapid HCV Antibody testing was followed by post-test counseling, confirmatory viral load testing, and linkage to care.

Results: Between 4/23/13 and 6/19/14 we conducted 1,634 rapid tests at 4 clinic sites and 17 alcohol and drug treatment programs. 300 rapid tests (18.4%) were positive. 288 Anti-HCV positive patients had confirmatory viral loads drawn with 214 (74.3%) positive and 74 (25.7%) undetectable. Of the 300 Anti-HCV positive patients, 208 (69.3%) were male and only 101 (33.7%) fell within the 'baby boomer' birth cohort of birth year between 1945-1965. 258 (86%) disclosed a prior history of injection drug use with 167 (55.7%) endorsing use within 12 months. The median age was 42 (range 20-72). 108 of 300 (36%) had insurance, and of these 91 (84.3%) were publicly funded. 150 of 214 patients with a positive HCV viral load (70.1%) were linked to care and evaluated by an experienced HCV treater. Frequency of HCV genotypes was similar to published literature except for a higher-than-expected number of GT-3 (17.4%). Roughly 10% of evaluated patients had an APRI score > 1.5 indicating advanced fibrosis on presentation to care. 38 of 81 patients (46.9%) who had a Rheumatoid Factor measured had positive results. 4 patients are currently on HCV therapy, 1 has completed therapy and is awaiting results, and 3 have achieved SVR12. Many more are in care and awaiting payer approval for treatment.

Supported by CDC FOA FS12-1209FFHP12



Age Distribution of Anti-HCV Positive Individuals by Gender (N = 300)

Conclusions: This demonstration project reports a high seroprevalence of HCV in urban community health centers and alcohol and drug rehabilitation centers. Only 36% of all Anti-HCV positive patients had insurance at the time of testing, and even those with insurance faced many barriers to accessing treatment. Despite robust outreach, testing, and linkage to care, uptake and coverage of HCV therapy in this largely poor, underserved, publicly-funded cohort remained low.

WEDNESDAY, FEBRUARY 25, 2015

Session P-N5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HCV: Epidemiology and Case Detection

662 Hepatitis C and B Testing Among HIV-Infected Individuals in England

Sam Lattimore; Sarah Collins; Celia Penman; Lukasz Cieply; Sema Mandal
Sentinel Surveillance of Blood-Borne Virus Testing
Public Health England, London, United Kingdom

Background: The British HIV Association guidelines for the management of hepatitis viruses in HIV-positive adults, recommend testing for hepatitis, B and C at HIV diagnosis, and annual thereafter. The sentinel surveillance of blood borne viruses collects laboratory data irrespective of test result; providing information on the population undergoing HIV and hepatitis testing at 15 sentinel laboratories.

Methods: Demographic information and HBV and HCV testing histories for persons newly diagnosed with HIV between 2008 and 2013 were extracted from the laboratory information systems of 15 sentinel laboratories in England. Service type and age at HIV diagnosis was recorded. Ethnicity was assigned using name analysis software. Duplicate records, reference testing and individuals aged <16 years at HIV diagnosis were excluded. Characteristics of individuals tested and testing positive for HIV, HBV and HCV were described. Data were managed in MS Access and analysed in R (CRAN).

Results: In total, 1,936,792 persons were tested for HIV across all settings, of whom 17,962 (0.9%) tested positive. Two thirds of all HIV positive persons were male (12,228/17,691) and where known, three quarters were white ethnic origin (75.9%; 6426/8463). Overall, 75.8% (13,412) of HIV positive persons were tested for anti-HCV, of whom 5.9% (797) tested positive. Of anti-HCV positive persons, 86.3% (688) were tested for HCV-RNA, of whom 75.9% (522) were positive indicating an active infection.

HCV genotype information was available for 73.3% (383) of all HCV-RNA positive persons. Genotype 1 infections were the most prevalent (61.8%; 237), followed by genotype 3, genotype 4 and genotype 2, representing 23.7%, 12.0% and 2.5%, respectively. HCV genotype distribution did not vary significantly by gender (χ^2=1.64; p=0.57), or by age group, but did vary by ethnic group (χ^2=19.84; p=0.02).

Overall 72.4% (13,011) of HIV positive persons were tested for HBsAg, of whom 4.5% (591) tested positive, of whom 62% (372) were tested for HBV DNA, of whom 84.9% (315) tested positive.

Conclusions: Approximately three-quarters of persons newly diagnosed with HIV were tested for HCV and HBV. Of these 522 and 591 persons were identified as being HIV/HCV and HIV/HBV co-infected, respectively. These findings suggest that while screening rates for HCV and HBV are high, further work is necessary to monitor and improve testing rates, and reduce the significant contribution of HCV and HBV towards hepatic morbidity and mortality in HIV infected individuals.

663 WITHDRAWN

664 HCV 2k/1b Recombinant Form among Hepatitis C–Infected Genotype 2 Patients in Georgia

Marika Karchava[1]; Jesper Waldenstrom[2]; Monica M. Parker[3]; Renee Hallack[3]; Lali Sharvadze[1]; Lana Gatserelia[1]; Nikoloz Chkhartishvili[1]; Natia Dvali[1]; Helen Norder[2]; Tengiz Tsertsvadze[1]
[1]*Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi, Georgia;* [2]*Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden;* [3]*Wadsworth Center, Albany, NY, US*

Background: The first HCV recombinant form, RF2k/1b was initially described in Russia and has since been identified from patients in Ireland, France, Estonia, Uzbekistan and Cyprus. Many of these patients were originally from the country of Georgia. Full genome sequencing studies revealed that this form shares the structural part of the HCV genome from genotype 2 and the non-structural part from genotype 1. As the routine method for genotype identification in Georgia is by the Versant HCV Genotype v2 kit, which amplifies structural Core and 5'UTR regions, nucleotide sequences in non-structural regions will be missed.Therefore, we conducted a small study to compare two genomic regions of HCV for the purpose of HCV recombinant form identification.

Methods: We retrospectively sequenced HCV non-structural region 5B (NS5B) in remnant specimens collected from 72 HCV infected Georgian patients with genotypes previously determined with the Versant HCV Genotype v2 kit as: 32 (44.4%) genotype 1, 21 (29.1%) genotype 2 and 19 (26.3%) genotype 3. Of those patients thirty six patient had underwent PEG/RBN treatment.

Results: A portion of the NS5B region was sequenced among all 72 specimens, with concordant non-structural/structural results for most genotype 1 and all genotype 3 specimens. Of 21 genotype 2 specimens, 16 showed similarities to genotype 1b. A phylogenetic tree shows that 15 sequences of discordant sequences formed a clade with RF2k/1b reference sequences chosen from different countries. Remaining discordant sequence was found outside the RF2k/1b sub-branch and formed a cluster within genotype 1b. Our findings reveal that among Georgian patients with HCV genotype 2, 76.1% of viral sequences were similar to genotype1b and phylogenetically distinct from genotype 2.

.

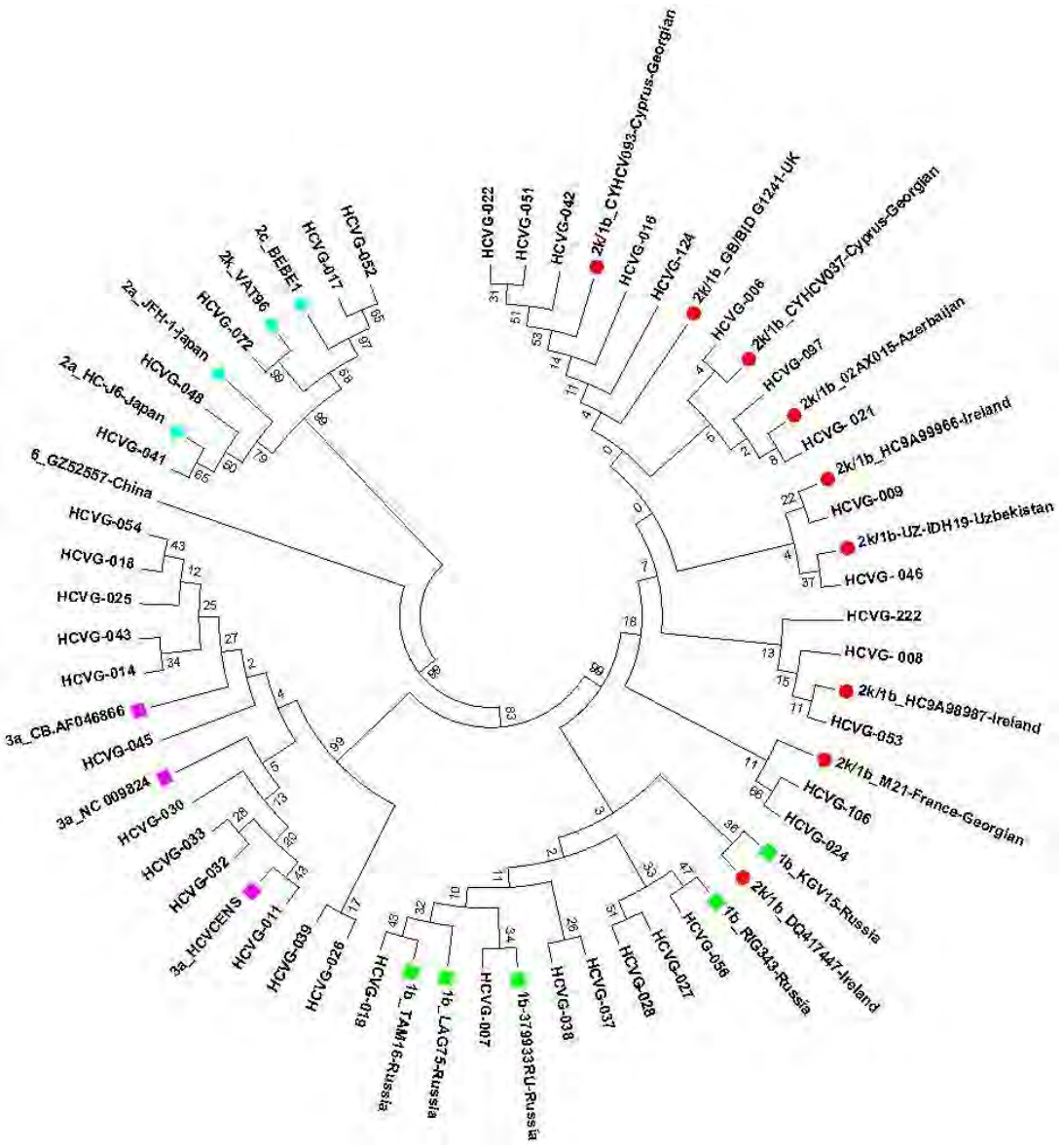


Figure 1. Phylogenetic Tree Constructed Based on the Partial Segment of the NS5B Region.

Reference recombinant strains RF 2k/1b in shown red diamond, genotype 1 in green, genotype 3 in purple and 2 in blue. Reference sequences are shown by their isolate name and country. Numbers at the nodes show the percentages of bootstrap values.

Conclusions: Since 21 specimens were considered genotype 2 based on standard HCV genotyping methods; there is a need for genotyping in two genomic regions at least for genotype 2. The high prevalence of possible RF2k/1b in our small sample group stresses the need of further studies, as this form might circulate in Georgia widely and may alter treatment options and/or duration as it shares non-structural regions with genotype 1 and may be as difficult to treat as this genotype

665 High HCV Prevalence Among Baby Boomers in Surveillance-Identified High HIV Risk Areas

Irene Kuo[1]; Meriam Mikre[1]; A. Toni Young[2]; Geoffrey Maugham[2]; Amanda D. Castel[1]

[1]George Washington University, Washington, DC, US; [2]Community Education Group, Washington, DC, US

Background: Despite advances in HCV screening, treatment, and recommendations, approaches for conducting HCV screening among baby boomers have not been fully explored. Because of the lack of hepatitis surveillance data and given shared risk factors for HIV and HCV, we used a novel method of identifying high HIV risk census tracts (CTs) using HIV surveillance data to target community-based HCV testing. We conducted a pilot study to estimate HCV seroprevalence and identify new and out of care HCV-seropositive baby boomers in these areas.

Methods: Between August-September 2014, we conducted community-based HCV rapid testing (OraQuick Rapid HCV Antibody Test) in Washington, DC in high risk CTs identified using an algorithm utilizing routinely reported HIV surveillance data incorporating HIV prevalence and suboptimal HIV care continuum outcomes (e.g., high community viral load and proportions of persons never in/out of HIV care). HCV testing was done by street outreach in the 12 highest ranking CTs. Eligible participants were born between 1945-1965 and not currently engaged in HCV care. Confidential testing and a face-to-face behavioral survey were conducted in a mobile unit or at a local community-based organization office. HCV antibody (HCVAb)-positive individuals were asked to provide a blood specimen for confirmation and referred to HCV care. Confirmatory testing is ongoing, and seropositive participants will be followed prospectively for 3 months to assess linkage to care. We report seroprevalence and baseline behavioral data using frequencies, chi-square and t-tests.

Results: Of 197 participants, 94% were black, mean age was 55 (SD±5), 74% were male, and 73% had public health insurance (see Table). 30% had ever injected drugs, 14% had ever been incarcerated, and 24% had ever been tattooed. 76% had never tested for HCV before. Overall, 59 (30%) were HCVAb-positive. 30% knew their HCV status but were not

receiving care; 70% were newly identified, of whom 51% had never been HCV tested before. HCV-seropositive individuals were older than negative individuals and were more likely to have ever injected drugs and have a history of incarceration (Table).

Table: Characteristics of baby boomer individuals (born 1945-1965) testing for HCV in high HIV risk census tracts, Washington, DC

Characteristic	Total N=197 (%)	HCVAb-positive n=59 (%)	HCVAb-negative n=138 (%)	Chi-squre P-value
Race – black	188 (93.9)	56 (94.9)	129 (93.5)	0.70
Mean age (±SD)	55 (±4.9)	57.0 (±4.9)	55.5 (±4.8)	**0.05***
Male gender	145 (73.6)	44 (74.6)	101 (73.2)	0.08
Public insurance	143 (72.6)	45 (76.3)	98 (71.0)	0.66
Ever injection drug use	60 (30.4)	47 (79.7)	13 (9.4)	**<0.0001**
Ever incarcerated	28 (14.2)	16 (27.1)	12 (8.7)	**0.001**
Ever received tattoo	46 (23.5)	18 (30.5)	28 (20.3)	0.25
Binge drank in past 12 months	54 (27.4)	17 (28.8)	37 (26.8)	0.77
Never been tested for HCV before	149 (75.6)	35 (59.3)	114 (82.6)	**0.001**
Never been told have HCV	167 (84.8)	41 (69.5)	126 (91.3)	**<0.0001**

* P-value derived from t-test.

Conclusions: Conducting community testing using this algorithm yielded a high HCV seroprevalence and large number of newly identified/out of care seropositive baby boomers. A high proportion had never been HCV tested, suggesting this testing paradigm may be effective in reaching individuals potentially at high risk for HCV in a community-based setting.

666 Low HCV Screening Uptake of the Current Birth Cohort Testing Guidelines

Alexander G. Geboy[1]; Hyun A. Cha[1]; Idene E. Perez[1]; Matthew T. Bell[1]; Sandeep Mahajan[2]; Adebisi O. Ayodele[2]; Dawn A. Fishbein[2]

[1]MedStar Health Research Institute, Hyattsville, MD, US; [2]MedStar Washington Hospital Center, Washington, DC, US

Background: The CMS recently supported the CDC and USPSTF grade B recommendation, and now covers a single HCV screening test if ordered by a primary care provider (PCP) to screen all persons born 1945-1965 (Birth Cohort) given a 3.25% prevalence rate. Previously published HCV rates of 2.5% in all persons in Washington, DC, and other urban areas, will likely increase with expanded testing.

Methods: In December 2012, we established a HCV testing program in the Primary Care Clinic at MedStar Washington Hospital Center, with CDC grant funding, to enhance testing for HCV infections among the Birth Cohort and not previously aware of their infection, link to care, and provide counseling, treatment and preventative services. Eligibility includes: born 1945-1965, without predetermined risk factors listed in the medical record, and not previously HCV tested or positive. HCV antibody positive (Ab+) patients are linked to care with Infectious Disease or Gastroenterology regardless of RNA status. Results reflect enrollment data from both the original grant and additional an CDC grant for expanded testing.

Results: As of September 23, 2014, 7.8% of the 1875 tested were HCV Ab+, 54% HCV RNA+, and this was no different from the first grant. Mean age of HCV Ab+ was 59.9 $\pm$ 5.6 years; 53.1% were men, and 76% had public insurance (Medicare or Medicaid); 85% of those tested, and 93% of those HCV Ab+ were black (13% b/AA men, 6% b/AA women). Those HCV Ab+ were more likely to be men (OR 1.9 [CI_{95} 1.1-3.4]) and have public insurance (OR 2.8 [CI_{95} 1.9-4.1]) than HCV Ab -. Unique primary care clinic appointments for those eligible (1st documented visit identified in the EMR) were 4016: 1248(31%) were tested, 974(24%) were missed (not tested but completed appointment), and 1794(45%) either canceled or no-showed.

Conclusions: The HCV Ab+ prevalence rate of 7.8% remained consistent over the two years and is significantly higher than the CDC Birth Cohort rate of 3.25% and the Washington, DC rate of 2.5%, although the latter reports all ages. Overall screening uptake, however, remains low at 24%. Given these high prevalence rates, new CMS recommendations, and improved therapeutic options available, testing initiatives in Primary Care settings need to be more rigorously upheld, and internal champions are needed to advocate for increased screening to ensure linkage to care and engagement within the HCV care cascade.

667 Evaluation of CDC Recommendations for HCV Testing in an Urban Emergency Department

Yu-Hsiang Hsieh[3]; Richard Rothman[3]; Oliver B. Laeyendecker[2]; Gabor Kelen[3]; Ama Avornu[3]; Eshan U. Patel[2]; Jim Kim[3]; Risha Irvin[3]; David L. Thomas[3]; Thomas C. Quinn[2]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]National Institute of Allergy and Infectious Diseases, Baltimore, MD, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: In 2012, with a national HCV prevalence of 3.25% among "baby boomers" (born 1945-65), CDC recommended one-time HCV testing without regard to risk in this cohort, in addition to targeted testing for all with risk factors or clinical indications. Emergency departments (EDs) are a key venue for HCV testing because of their success in HIV screening given the populations they serve. However, few EDs have evaluated the underlining burden of known and unknown HCV infections in their populations before implementing an HCV testing program. Since the Hopkins ED has conducted serosurveys on HCV and HIV for the past two decades, we sought to determine the overall burden of undocumented HCV infection in our inner-city ED in order to provide guidance for an ED-based HCV testing program.

Methods: An 8-week seroprevalence study with identity-unlinked methodology was conducted in an urban adult ED in 2013. All patients with blood specimens as part of their clinical procedures were included. Demographic and clinical information including documented HCV infection was obtained from administrative datasets or from electronic medical records. Anti-HCV antibody testing was performed on excess blood samples by HCV EIA after de-identification.

Results: Of 4,687 patients, 650 (14%) were anti-HCV antibody positive. Of these, 203 (31%) patients did not have documented HCV infection. "Baby boomer" patients v. others had a higher overall and undocumented HCV prevalence (overall: 24.9% vs. 7.1%; unknown: 7.2% vs. 2.6%, $p<0.05$). Prevalence of undocumented HCV infection varied by age, gender, and race (Figure 1). Notably, the undocumented prevalence for non-Black male born after 1965 and Black men and women born between 1966 and 1977 was equal to or greater than national prevalence of 3.25% in the "baby boomer" birth cohort. Among patients with undocumented infections, 37% occurred outside the "baby boomers" cohort. Injection drug use (IDU) was reported in only 30% of patients with undocumented HCV born after 1965. If our ED adhered to the CDC guidelines, 55 (27%) patients with undocumented HCV would not be screened.

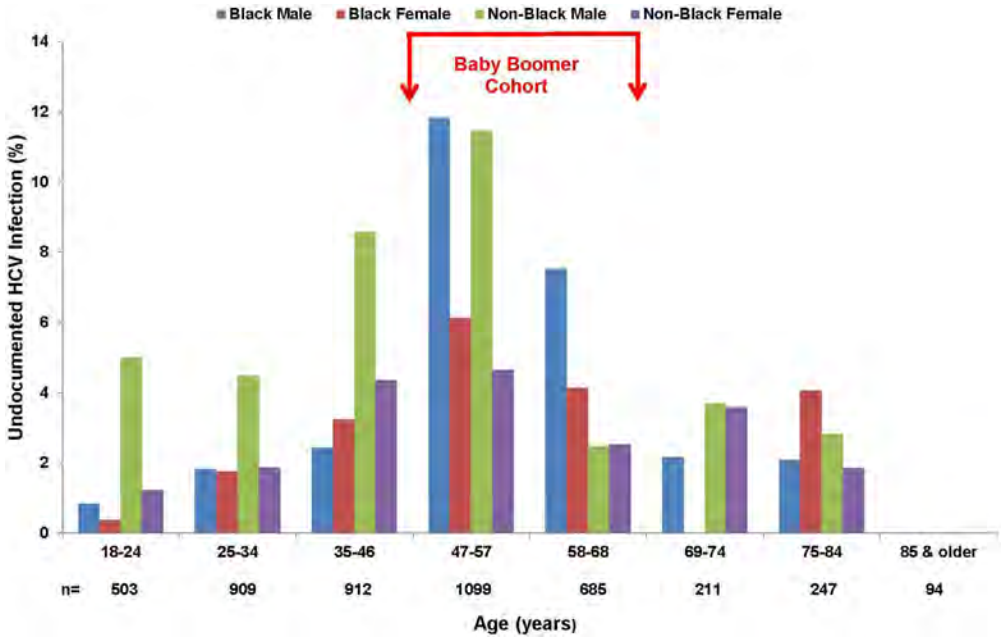


Figure 1: Prevalence of Undocumented HCV Infection by Age, Race and Gender Group in 4,687 Johns Hopkins Hospital Adult Emergency Department Patients, 2013

Conclusions: High seroprevalence of both known and undocumented HCV infection were observed, indicating that urban EDs could be a useful venue for HCV testing. Our data also demonstrated that high seroprevalence was also observed among subgroups of non-"baby boomer " patients without IDU, suggesting the need to consider for modification of the CDC recommendations for HCV testing in the ED settings.

668 Impact of Integrating EMR HCV Testing Prompts in a Difficult to Navigate EMR System

Stephanie Tzarnas[2]; Monique Allen[2]; Allison Brodsky[2]; Gregory Johnson[2]; Lora Magaldi[2]; Carolyn Moy[2]; Nancy Tursi[2]; Steven Zivich[2]; Stacey Trooskin[2]

[1]Drexel University College of Medicine, Philadelphia, PA, US; [2]Drexel University College of Medicine, Philadelphia, PA, US; [3]Drexel University College of Medicine, Philadelphia, PA, US; [4]Drexel University College of Medicine, Philadelphia, PA, US

Background: At least 50% of individuals infected with HCV are unaware of their status. Furthermore, 50% of individuals with a reactive antibody test never receive a confirmatory test. Electronic Health Record (EHR) testing prompts that reflect CDC recommendations for birth cohort testing and the standard HCV screening algorithm have the potential to be a useful tool. We aim to describe the impact of these EMR modifications on primary care provider (PCP) testing practices.

Methods: EHR prompts began July 1 2014. Individuals born between 1945-1965 with no prior HCV testing had a prompt added that appeared under the patient's name reminding the PCP that the "Patient Needs HCV Screening". Any patient with a reactive antibody test or an ICD-9 code consistent with chronic HCV infection but no confirmatory test had a similar prompt added reminding the PCP that the "Patient needs HCV confirmatory testing". Educational sessions about CDC screening guidelines, testing algorithms and prompts were held at primary care practices to reinforce implementation. To simplify HCV test ordering options EHR technical staff removed orders for non-preferred tests such as older tests and redundant tests. Technical staff limited access to duplicate testing options. Providers were encouraged to use HCV antibody testing with reflex to PCR quantitative testing as the preferred method.

Results: Baseline data in May showed that 6.9% of the 1,658 birth cohort patients seen were tested for HCV. Of those tested, 18% were tested using non-preferred testing methods and only 4.4% were tested using the preferred method. June showed that 12% of the 1,609 birth cohort patients seen were tested for HCV; 8.7% were tested using non-preferred tests and 5.9% using the preferred test. After prompts went live in July, 18% of the 1,807 birth cohort patients seen were tested for HCV, only 2% were tested using the non-preferred tests and 42% were tested using the preferred test. In August 19.7% of the 1,628 birth cohort patients seen were tested, only 0.76% were tested using non-preferred tests and 59% were tested using the preferred test.

Conclusions: Prompts implemented in July were effective in increasing routine screening of the baby boomer birth cohort. There was a shift towards ordering tests that support the recommended testing algorithm. EHR prompts and provider education have the potential to increase the number of individuals aware of their HCV status.

WEDNESDAY, FEBRUARY 25, 2015

Session P-N6 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Acute HCV Infection

669 SVR12 Results After 12w Boceprevir + P/R in the Dutch Acute Hepatitis C in HIV Study

Sebastiaan J. Hullegie[8]; Mark A. Claassen[8]; Guido E. van den Berk[2]; Jan T. van der Meer[1]; Joop E. Arends[3]; Clemens Richter[4]; Dirk Posthouwer[5]; Peter P. Koopmans[6]; Fanny N. Lauw[7]; Bart J. Rijnders[8]

[1]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [2]Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands; [3]University Medical Center Utrecht, Utrecht, Netherlands; [4]Rijnstate Ziekenhuis, Arnhem, Netherlands; [5]Maastricht University Medical Center, Maastricht, Netherlands; [6]Radboud University Medical Center, Nijmegen, Netherlands; [7]Slotervaart Ziekenhuis, Amsterdam, Netherlands; [8]Erasmus University Medical Center, Rotterdam, Netherlands

Background: The international epidemic of acute hepatitis C virus (AHCV) continues to spread within HIV+ men having sex with men (MSM), with incidence rates reported between .08 and 1.75%. Relatively high cure rates (60-70%) are achieved with 24 weeks of peginterferon(P) (+/- ribavirin(R)). The addition of a direct-acting anti-viral drug (DAA)

may lead to higher cure rates and may allow for a shorter treatment duration. Here we present an interim analysis of the first 27 patients treated in the DAHH-Study, evaluating the efficacy and tolerability of a 12-week boceprevir, P+R regimen in AHCV genotype 1 infections in 10 participating Dutch hospitals.

Methods: HIV+ patients visiting the outpatient clinic with a new ALAT rise above the upper limit of normal were screened for the presence of HCV RNA. If positive, stored historical plasma samples (within 6 months) were tested to prove that the HCV infection was recent. Boceprevir, P+R for 12 weeks was started without a P+R lead-in and was initiated no later than 26 weeks after the presumed day of infection. Primary endpoint is sustained viral response at week 24(SVR24) in patients with no HCV RNA detected (Roche, CAP/CTM) at w4(RVR4) and in all patients included(secondary endpoint).

Results: Since September 2013 we screened 104 HIV+ patients with a new HCV infection. We excluded 42 patients because of genotype 4 (n=17), HCV infection >6 months (n=11), spontaneous clearance (n=6) and refusal to participate (n=8). Twelve patients are currently awaiting clearance. Fifty were included of which 37 have started therapy at abstract submission. RVR4 was reached in 23/33 (70%) patients with end of treatment (EOT) responses being 26/29 (90%). SVR12 was 18/19 (95%, 95% CI 72%-99%) in the RVR4 population. SVR12 was 21/27 (78%, 95% CI 57%-91%) in patients regardless of RVR4 results. Updated SVR12 data of the first 35 patients will be presented at the congress.

Conclusions: Addition of boceprevir to P+R for AHCV treatment results in SVR12 rates of 95% (95% CI 72%-99%) with a 50% shorter therapy duration as long as HCV RNA has become negative at w4. Regardless of RVR4 the SVR12 is comparable with 24 weeks P+R (78%, 95% CI 57%-91%). The DAHHS network allows for a fast and accurate evaluation of new DAA for the treatment of AHCV in a significant number of patients.

670 Does the Availability of New DAAs Influence Treatment Uptake in Acute Hepatitis C in HIV Coinfection?

Christoph Boesecke[1]; Mark Nelson[2]; Patrick Ingiliz[5]; Thomas Lutz[3]; Stefan H. Scholten[4]; Christoph D. Spinner[6]; Michael Rausch[9]; Thomas Reiberger[7]; Stefan Mauss[8]; Jürgen Rockstroh[1]

[1]Bonn University Hospital, Bonn, Germany; [2]Chelsea and Westminster Hospital, NHS Foundation Trust, London, United Kingdom; [3]Infektiologikum, Frankfurt/Main, Germany; [4]Praxis Hohenstaufenring, Cologne, Germany; [5]MiB, Berlin, Germany; [6]Interdisciplinary HIV Centre (IZAR), University Hospital Klinikum Rechts der Isar, Munich, Germany; [7]Medical University of Vienna, Vienna, Austria; [8]Center for HIV and Hepatogastroenterology, Duesseldorf, Germany; [9]Aerztezentrum Nollendorfplatz, Berlin, Germany

Background: With the availability of newer DAAs for treatment of chronic hepatitis C infection (HCV) HCV therapy has become considerably less toxic and even more successful than treatment of acute hepatitis C infection (AHC) with pegylated interferon (pegIFN) and ribavirin (RBV). Current DAA-based regimens are not approved for treatment of AHC and thus, also not reimbursed.

Here we evaluate potential changes in the annual rates of treatment initiation in Europe for AHC coinfection in the DAA era.

Methods: The PROBE-C study is an observational European cohort on AHC in HIV coinfection. Between 2007-2014 483 AHC episodes were documented in 461 HIV-infected patients from Austria, Denmark, France, Germany, Great Britain and Spain. Fisher's exact, chi-square and Mann-Whitney U test were used for statistical analysis.

Results: All patients were male, median age was 41 years. Main routes of transmission were MSM (97.4%) and IVDU (2.6%). 77.4% of patients were infected with HCV GT1 and 18.9% with GT4. Median baseline HCV-RNA was 2.019.500IU/mL and median CD4+ T cell count 478 cells/µL. 93% of all patients received cART, 86% had baseline suppressed HIV-RNA (<200copies/mL). Median ALT was 388 U/l.

In 60/483 (12.6%) episodes AHC resolved spontaneously, in 309/483 (64%) treatment with pegIFN/RBV was initiated within 24 weeks of AHC diagnosis. Median time from diagnosis to treatment initiation was 8 weeks. SVR rate was 70%.

Overall, as shown in table 1 there was an increase in treatment initiation for AHC from 2007-2012. However, since 2012 an annual decline from 76% to 45% was observed. There was no association between treatment initiation and HCV transmission risk, HCV GT, HCV RNA levels nor baseline ALT.

Table 1. Annual rates of treatment initiation for new AHC diagnoses from 2007 to 2014

Year	2007	2008	2009	2010	2011	2012	2013	2014
Treated uptake per newly diagnosed AHC episodes (%)	7/15 (46.7)	15/30 (50)	26/40 (65)	35/49 (71.4)	66/105 (62.9)	82/108 (76)	64/105 (61)	14/31 (45)
Relative change in treatment uptake	N/A	+3.3%	+15%	+6.4%	-8.5%	+13.1%	-15%	-16%

Table 1. Annual rates of treatment initiation for new AHC diagnoses from 2007 to 2014

Conclusions: Treatment uptake for AHC has substantially decreased in the last 2 years potentially reflecting patients' and/or physicians' wish for a short, well-tolerated and highly successful DAA-based therapy which to date is only approved and reimbursed for treatment of chronic HCV infection. However, when treatment during AHC is withhold, more patients remain viremic, which then may foster the epidemic of AHC among HIV-infected MSM. Therefore, studies evaluating safety and efficacy of IFN-free DAA regimens for AHC are urgently needed.

671 Long-Term Follow-Up of HIV-Positive Men Who Have Sex With Men (MSM) With Acute Hepatitis C Virus (HCV) Infection: High Rates of Treatment and Low Rates of Liver-Related Complications

Patrick Ingiliz[1]; Anders C. Boyd[3]; Katharina Steininger[1]; Andreas Carganico[1]; Stephan Dupke[1]; Ivanka Krznaric[1]; Marcel Schuetze[1]; Stefan Neifer[2]; Martin J. Obermeier[1]; Axel Baumgarten[1]

[1]Medical Center for Infectious Diseases, Berlin, Germany; [2]Microbiology Laboratory, Berlin, Germany; [3]INSERM UMR_S 1136, Paris, France

Background: Acute hepatitis C has been identified as a major factor of morbidity in HIV-infected MSM.

Interferon-based treatments have been extensively used in this population in Europe. However, benefits related to treatment remain unknown in this population, bringing into question the use of interferon in the era of directly acting antivirals.

Methods: Retrospective analysis of HIV-positive MSM with acute HCV infection from a single center in Berlin from 2002 to 2013. Liver fibrosis was estimated by transient elastography (Fibroscan®) and/or serum markers (Fibrotest®). The following endpoints were documented: significant fibrosis, cirrhosis, HCC, liver-related death, liver transplant, non-liver-related death. Risk-factors for significant fibrosis and liver cirrhosis were determined using a proportional hazards regression model with death as a competing risk.

Results: 207 cases of acute hepatitis C occurred in 174 MSM. The median age was 39 years (IQR: 32-45), the median CD4 count was 514 mm^3 (IQR: 386-675), the maximum ALT level was 416 U/L (IQR: 157-868). Most patients were genotype 1a (79%), and genotype 4 (11%). A total of 22/207 (10.6%) acute infections cleared spontaneously, which was

significantly associated with lower HCV-RNA and higher maximum ALT levels ($p<0.001$). Out of 185 infections without spontaneous clearance, 161 (87.0%) were treated with interferon-based therapy, among whom 103/161 (64.0%) achieved sustained virological response. Patients were followed-up for a median time of 48 months (IQR: 29-81). Overall, 12 (6.9%) patients were diagnosed with liver cirrhosis after 13.9 months (IQR: 6.4-40.7) and 11 deaths (5.3%) occurred during the observation period. Causes of death were as follows: AIDS (n=2), cardiovascular events (n=4), drug overdose/suicide (n=2), or other (n=3). No liver-related deaths or liver transplants occurred. In multivariable analysis, the number of reinfections increased the risk of developing significant fibrosis (adjusted-HR=2.89; 95%CI=1.90-4.39). Non-response to interferon-based treatment was the only significant determinant for increased risk in liver cirrhosis (HR=5.47; 95%CI=1.46-20.53).

Conclusions: Over the past decade, interferon-based treatment of HCV infection has provided sustained virological response for many HIV-positive MSM with acute HCV infection. However, the fact that severe outcomes were rare suggests that patients may wait for newer regimens with fewer side effects.

672 Hepatitis C in Men Who Have Sex with Men With New HIV Diagnoses in Los Angeles

Kara W. Chew[1]; Marjan Javanbakht[2]; Laurel Clare[1]; Lorelei Bornfleth[1]; Debika Bhattacharya[1]; Pamina Gorbach[2]; Martha L. Blum[3]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, US; [2]UCLA Fielding School of Public Health, Los Angeles, CA, US; [3]Community Hospital of the Monterey Peninsula, Monterey, CA, US

Background: Geographic and sociodemographic characterization of hepatitis C virus (HCV) transmission amongst men who have sex with men (MSM) has been limited. Our aim was to characterize HCV prevalence, risk factors for HCV co-infection, and patterns of HIV and HCV co-transmission and transmitted drug resistance mutations (DRMs) in newly HIV-diagnosed Los Angeles MSM.

Methods: We extracted viral RNA from stored plasma samples from the MetroMates cohort, a Los Angeles cohort of recently infected (within the past year) or newly diagnosed HIV-infected MSM with well-characterized substance use and sexual behavioral characteristics via ACASI surveys. Samples were screened for HCV by qPCR. HCV E1, E2, core, NS3 protease and NS5B polymerase and HIV-1 protease and reverse transcriptase (RT) regions were amplified and sequenced. Phylogenetic analysis was used to determine relatedness of HCV and HIV-1 isolates within the cohort. Protease and polymerase sequences were examined for DRMs, including the HCV mutations V36M/A, T54A/S, V55A, Q80K, R155K, A156S/T, D168T/V, I/V170A and S282T.

Results: Of 185 newly HIV-diagnosed MSM, the majority (65%) were of minority race/ethnicity and recently infected (57.8%). A minority (6.6%) reported injection drug use (IDU), whereas 52.8% reported recent substance use, primarily cannabis or stimulant use. High risk sexual behaviors included 74.6% with unprotected receptive anal intercourse, 32.4% group sex, and 5.7% fisting. One-third reported a history of recent sexually transmitted infection (STI). Only 3 (1.6%) subjects had detectable HCV RNA, two genotype 1a and one 3a. The HCV-positive subjects were slightly older, but not statistically significantly. Only 1 subject with HCV had a history of IDU. There were too few HCV infections to identify significant risk factors for HCV. One subject had an HIV RT mutation (K103N). None had clinically relevant NS3 or NS5B HCV DRMs. Amongst the 3 HCV-infected subjects, HIV and HCV sequences were unrelated by phylogenetic analysis.

Characteristics of the cohort overall and by hepatitis C status

Characteristic	Overall (n=185) Median (IQR) or n (%)	HCV-negative (n=182) Median (IQR) or n (%)	HCV-positive (n=3) Median (IQR) or n (%)
Age (years)	28.3 (24.7-35.0)	28.3 (24.7-34.8)	35.8 (22.3-45.1)
Race African-American Hispanic Asian White Other	32 (17.7) 89 (49.2) 5 (2.8) 47 (26.0) 8 (4.4)	31 (17.4) 87 (48.9) 5 (2.8) 47 (26.4) 8 (4.4)	1 (33.3) 2 (66.7) 0 (0) 0 (0) 0 (0)
Incarcerated, past 12 months	17 (9.3)	17 (9.5)	0 (0)
Substance use, past 3 months Any drugs Cocaine Methamphetamine Cannabis Inhalants Sedatives Hallucinogens Opioids	96 (52.8) 26 (14.3) 33 (18.1) 79 (43.4) 6 (3.3) 16 (8.8) 3 (1.7) 6 (3.3)	93 (52.0) 25 (14.0) 30 (16.8) 77 (43.0) 5 (2.8) 15 (8.4) 2 (1.1) 5 (2.8)	3 (100) 1 (33.3) 3 (100) 2 (66.7) 1 (33.3) 1 (33.3) 1 (33.3) 1 (33.3)
Injection drug use, past 12 months	12 (6.6)	11 (6.2)	1 (33.3)
Alcohol, any use, past 3 months	129 (70.9)	127 (71.0)	2 (66.7)
Number of sexual partners, past 12 months	9 (4.20)	9 (4-20)	6 (6-14)
Unprotected insertive anal intercourse, last 6 partners	115 (64.6)	113 (64.2)	2 (66.7)
Unprotected receptive anal intercourse, last 6 partners	132 (74.6)	130 (74.3)	2 (66.7)
Fisted by partner, last 6 partners	20 (10.8)	19 (10.6)	1 (33.3)
Group sex	60 (32.4)	58 (32.4)	2 (66.7)
Sexually transmitted infections, past 12 months Chlamydia Gonorrhea Syphilis HSV	69 (37.9) 57 (31.3) 57 (31.3) 11 (6.0)	68 (38.0) 64 (35.8) 56 (31.3) 11 96.2)	1 (33.3) 1 (33.3) 1 (33.3) 0 (0)
HIV viral load (copies/mL)*	41,538 (5,771-150,756)	41,518 (6,296-144,378)	60,476 (<50-155,000)
CD4 cell count (cells/mm3)*	553 (408-692)	553 (408-692)	Unavailable

*HIV viral load and CD4 measurements were collected after study enrollment, at which time some participants were on HIV antiretroviral therapy. CD4 cell counts were available for 80 subjects.

Conclusions: Prevalence of HCV co-infection was low and there was no evidence of HIV-HCV co-transmission in this cohort of relatively young, predominantly minority, newly HIV-diagnosed MSM, most with early HIV infection, with high rates of high risk sexual behaviors, STI, and non-IDU. The low HCV prevalence in these newly HIV-diagnosed MSM suggests HIV precedes HCV acquisition, and not the reverse, and presents an opportunity for targeted HCV prevention campaigns in this high-risk population.

673 Development and Comparison of Hepatitis C Cross-Sectional Incidence Testing Methods

Eshan U. Patel[1]; Andrea Cox[2]; Shruti H. Mehta[3]; Caroline E. Mullis[2]; Jeffrey Quinn[2]; Gregory D. Kirk[3]; Thomas C. Quinn[1]; Oliver B. Laeyendecker[1]

[1]National Institute of Allergy and Infectious Diseases (NIAID), Baltimore, MD, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

Background: The traditional method to determine hepatitis C (HCV) incidence requires longitudinal cohorts. However, cohort studies are challenging because they are expensive, time consuming, and may not achieve sufficient follow-up in high-risk populations such as people who inject drugs (PWIDs). The ability to detect recently infected individuals from a cross-sectional survey would reduce the need for longitudinal data. We present two HCV avidity-based tests for recent infection and compare testing algorithms to identify newly infected individuals.

Methods: Samples with previously determined HCV RNA levels from 72 PWIDs (396 samples) with known dates of infection from the Baltimore Before-and-After Acute Study of Hepatitis (BBAASH) cohort and 1,087 PWIDs (1,471 samples) infected for ≥2 years from the AIDS Linked to the Intravenous Experience (ALIVE) cohort were tested for HCV avidity by two assays: (1) the Ortho HCV 3.0 ELISA, treated with 0.25M diethylamine and (2) the Genedia HCV 3.0 ELISA, treated with 11M urea. The avidity index was the optical density ratio between treated and untreated wells. High precision of cross-sectional incidence estimation is characterized by a large mean duration of recent infection (MDRI), the average length of time that people with newly acquired infection are classified as recent, and a small false-recent rate (FRR), the proportion of non-recent infections misclassified as being recent. These properties were evaluated for 28 testing algorithms that included the two avidity assays alone at various cutoffs with and without viral load testing.

Results: At various avidity index cutoffs, the MDRI varied between 234.5–392.8 days for the Ortho 3.0 avidity assay alone and 74.5–354.0 days for the Genedia 3.0 avidity assay alone. Both avidity assays produced high FRRs, primarily due to individuals who spontaneously cleared the virus. The FRRs for the avidity assays decreased when evaluated in combination with HCV RNA confirmation, but remained above the ideal FRR of 0% (Table 1).

Table 1. Performance of the Ortho 3.0 and Genedia 3.0 HCV avidity assays with HCV RNA confirmation.

Avidity	Ortho 3.0 + HCV RNA Confirmation		Genedia 3.0 + HCV RNA Confirmation	
Index	**MDRI**, days (95% CI)	**FRR**, % (95% CI)	**MDRI**, days (95% CI)	**FRR**, % (95% CI)
20%	101.8 (82.9-124.8)	1.4 (0.7-2.6)	46.1 (31.3-64.9)	0.3 (0.1-0.8)
30%	125.6 (102.6-150.4)	2.2 (1.2-3.5)	66.4 (47.5-89.3)	0.9 (0.5-2.0)
40%	147.5 (123.1-175.2)	4.0 (2.7-5.8)	82.7 (62.8-105.8)	1.9 (1.2-2.7)
50%	158.4 (133.4-187.2)	5.0 (3.5-6.9)	98.8 (76.3-124.9)	4.0 (3.0-5.1)
60%	176.4 (149.5-204.3)	5.7 (4.1-7.7)	115.1 (91.3-139.6)	7.9 (6.5-9.4)
70%	191.3 (162.2-220.2)	7.3 (5.5-9.5)	148.1 (121.8-175.8)	12.7 (11.0-14.5)
80%	195.3 (166.8-225.4)	9.0 (7.0-11.4)	193.4 (162.2-222.8)	20.3 (18.2-22.4)
Cohort	BBAASH (n=396)	ALIVE (n=697)	BBAASH (n=396)	ALIVE (n=1,451)

Conclusions: The HCV avidity and viral load testing algorithms were able to identify recently infected individuals. However, further work is needed to determine additional biomarkers that will reduce the FRRs of these testing algorithms. Efforts to optimize cross-sectional HCV incidence testing will contribute to a more practical and timely method to determine rates of new infection, yielding more rapid assessment of the epidemic and of the impact of intervention efforts.

674 Risk Factors for Transmission of HCV Among HIV-Infected MSM: A Case-Control Study

Joost W. Vanhommerig[1]; Femke A. Lambers[1]; Janke Schinkel[2]; Joop E. Arends[3]; Fanny N. Lauw[4]; Kees Brinkman[5]; Luuk Gras[6]; Bart J. Rijnders[7]; Jan T. van der Meer[2]; Maria Prins[1]

[1]GGD Amsterdam, Amsterdam, Netherlands; [2]Academic Medical Center, Amsterdam, Netherlands; [3]University Medical Center Utrecht, Utrecht, Netherlands; [4]Slotervaart Hospital, Amsterdam, Netherlands; [5]OLVG Hospital, Amsterdam, Netherlands; [6]Dutch HIV Monitoring Foundation, Amsterdam, Netherlands; [7]Erasmus University Medical Center, Rotterdam, Netherlands; [8]Academic Medical Center, Amsterdam, Netherlands

Background: Since 2000, incidence of sexually acquired hepatitis C virus (HCV) infection has increased among HIV infected men who have sex with men (MSM). Only a few case-control and cohort studies evaluating transmission risk factors were conducted, and most of these studies initially were not designed to study HCV, but HIV-related behavior and characteristics. The MOSAIC study provides a unique opportunity to study risk factors for acute HCV infection in HIV-infected MSM.

Methods: From 2009 onwards, HIV-infected MSM with an acute HCV infection (cases) were prospectively included and followed at five hospitals in the Netherlands. For each case, one to two unmatched controls were recruited from the population of HIV-infected MSM without HCV. Written questionnaires were administered, covering socio-demographics, blood-borne risk factors for HCV infection, sexual risk behavior, and drug use. Clinical data on HIV-and HCV were acquired through linkage with databases from the Dutch HIV Monitoring Foundation. Determinants of HCV infection were analyzed using logistic regression.

Results: Among 213 MSM (82 MSM with and 131 MSM without HCV infection), median age was 45.7 years (IQR:41.0-52.2). Ulcerative STI (OR:5.26,95%CI:1.72-16.1), receptive unprotected anal intercourse (rUAI;OR:5.05,95%CI:1.63-15.6), sharing sex toys (OR:3.98,95%CI:1.12-14.2), sharing straws when snorting drugs (OR:3.46,95%CI:1.41-8.47), unprotected fisting (OR:2.54,95%CI:1.01-6.42), and CD4 cell count at the last HCV negative visit prior to study entry (OR:1.74 per cube root lower, 95%CI:1.18-2.56) were independently associated with HCV acquisition. Of interest, injecting drug use was reported by only 12 men, and was not significantly associated in multivariable analysis; nor were anal rinsing, rectal bleeding, number of sex partners, meeting location, and group sex participation. No interactions were found.

Conclusions: To our knowledge, this is the largest case-control study focusing on transmission of HCV among HIV-infected MSM. Besides known risk factors for HCV (rUAI, STI, fisting, and sharing of sex toys), associations between the sharing of straws when snorting drugs, and lower CD4 cell count and HCV acquisition were found. Our study confirms sexual transmission and a role of non-injecting drug use as a risk factor for HCV transmission. Further studies are needed on the role of CD4 cell count, as it is still unclear whether a lower CD4 cell count facilitates HCV infection or is a result of acute HCV infection itself (or both).

675 Behavioural and Treatment Interventions to Reduce HCV Transmissions in HIV+ MSM

Luisa Salazar-Vizcaya[1]; Roger Kouyos[2]; Cindy Zahnd[1]; Manuel Battegay[3]; Katharine Darling[4]; Alexandra Calmy[5]; Pietro L. Vernazza[6]; Olivia Keiser[1]; Andri Rauch[7]
On behalf of the Swiss HIV Cohort Study

[1]University of Bern, Bern, Switzerland; [2]University Hospital Zurich, Zürich, Switzerland; [3]University Hospital Basel, Basel, Switzerland; [4]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [5]Geneva University Hospitals, Geneva, Switzerland; [6]Kantonsspital St Gallen, St Gallen, Switzerland; [7]University Hospital Bern, Inselspital, Bern, Switzerland

Background: The incidence of hepatitis C virus (HCV) infections among HIV-infected men who have sex with men (MSM) increased markedly in industrialized countries and is associated with high risk sexual behaviour including traumatic sex. Finding the most effective interventions to control this epidemic is key to reducing liver-related morbidity and mortality in these patients. HCV treatments with direct-acting antivirals (DAAs) achieve high cure rates, but the role of these therapies on reducing HCV transmission remains uncertain.

Methods: Based on behavioural, epidemiological and clinical information collected prospectively in the Swiss HIV Cohort Study (SHCS), we developed a deterministic mathematical model for sexually transmitted HCV infections among HIV-positive MSM in Switzerland. We reproduced the epidemic for the period 2000-2013 and estimated the basic reproductive number R_0. We then evaluated the effects of increasing treatment uptake (5-fold increase from the currently observed treatment rate of 0.22/person-year), or of increasing treatment efficacy on reducing the future HCV incidence. Finally, we evaluated the impact of three scenarios of future unsafe sex frequency on HCV incidence.

Results: The best-fit parameter values indicated that the HCV epidemic was mainly driven by the increase in sexual risk behaviour in recent years. The epidemic threshold ($R_0 = 1$) was crossed in 2010. A pessimistic scenario assuming that the frequency of unsafe sex continues to rise predicts a steep increase in HCV incidence, with little differences between treatment strategies (Figure). A scenario where the frequency of unsafe sex remains stable results in declining HCV incidence with or without DAA therapy, provided that treatment rate increases considerably. The optimistic assumption that the frequency of unsafe sex reduces considerably leads to an immediate and steep decrease in the future HCV incidence, even in the absence of improvements in treatment rate and/or efficacy (Figure).

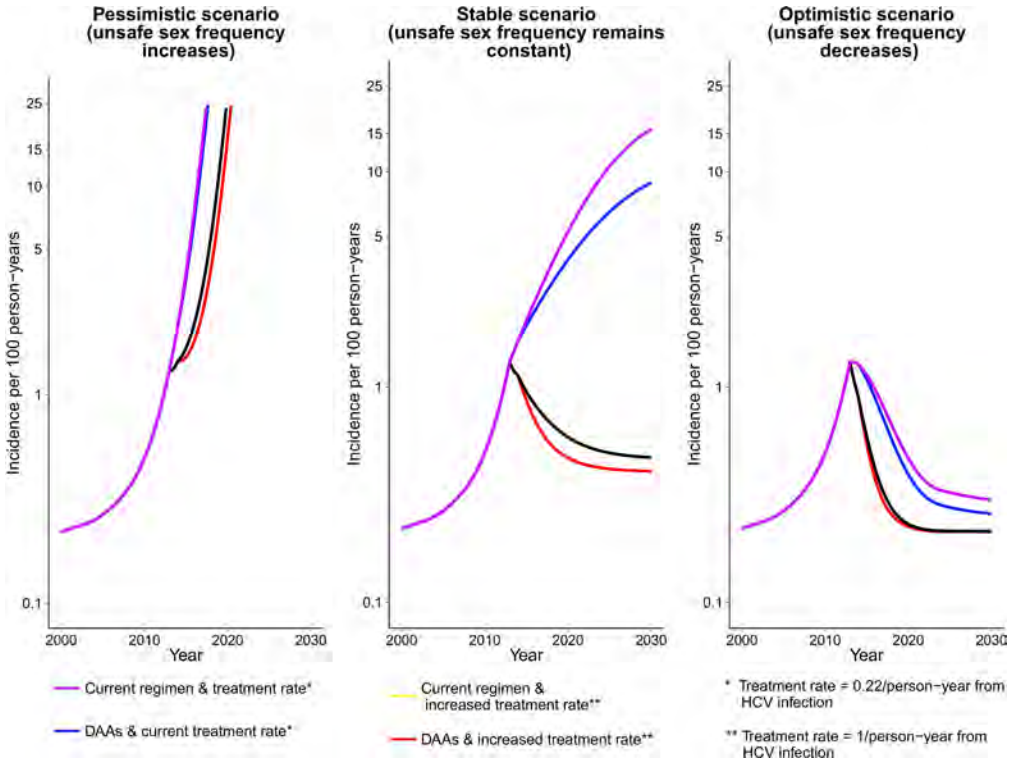


Figure. Projected HCV incidence in HIV-infected MSM assuming different treatment and behavioural scenarios.

Conclusions: Treatment interventions are only effective in reducing HCV transmission among HIV-infected MSM if the frequency of high risk sexual behaviour does not increase as in recent years. However, if unsafe sex behaviour stabilizes, increased treatment uptake and efficacy are predicted to curb the epidemic within 10 years.

WEDNESDAY, FEBRUARY 25, 2015

Session P-N7 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Immunopathogenesis of HCV Infection

676 Macrophage Activation and Hepatitis C (HCV) Disease Progression in HIV-Infected Women Participating in the Women's Interagency HIV Study (WIHS)

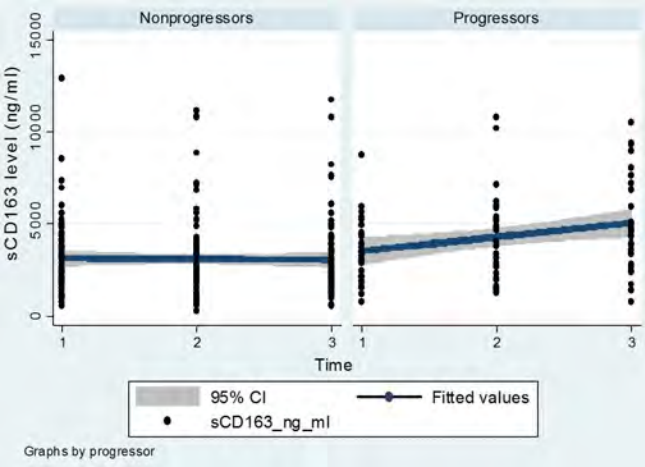
Audrey L. French[1]; Charlesnika Evans[3]; Marion G. Peters[2]; Mary A. Young[4]; Mark Kuniholm[6]; Michael Augenbraun[7]; Seema N. Desai[5]

[1]CORE Center/ Stroger Hospital of Cook County, Chicago, IL, US; [2]University of California San Francisco, San Francisco, CA, US; [3]Northwestern University, Chicago, IL, US; [4]Georgetown University, Washington, IL, US; [5]Rush University Medical Center, Chicago, IL, US; [6]Montefiore Medical Center, University Hospital for Albert Einstein College of Medicine, Bronx, NY, US; [7]State University of New York Downstate, Brooklyn, NY, US

Background: Hepatic macrophage activation by endotoxin is thought to contribute to hepatic fibrosis in HCV infection. We measured changes in markers of macrophage activation, microbial translocation and inflammation in HIV/HCV co-infected women comparing women who had rapid liver disease progression to liver disease non-progressors.

Methods: Soluble CD163 and CD14, lipopolysaccharide (LPS), tumor necrosis factor receptor II (TNFRII), chemokine ligand-2 (CCL2) and interleukin-6 (IL-6) were measured by ELISA at 3 timepoints (T) on stored serum from HIV/HCV infected women. Women were retrospectively defined as liver disease progressors (LDP) or non-progressors (NP).). T1 for all women was a visit at which serum markers (APRI and FIB-4) or liver biopsy were consistent with no/minimal fibrosis. T3 was approximately 5 years after T1. For NP, biopsies or fibrosis markers continued to reflect minimal or no fibrosis at T3. Progressors had severe fibrosis by histology, imminent liver-related death or both serum markers consistent with cirrhosis/significant fibrosis at T3. T2 was ~equidistant between T1 and T3. Women with any hazardous alcohol consumption (≥7 drinks/week) between T1 and T3 were excluded.

Results: Soluble markers were measured in 31 liver disease progressors and 84 non-progressors. The median time between the T1 and 3 was 4.9 years. Median age, CD4 and HIVRNA at T1 for LDP and NP were 42 and 40 years, 462 and 487 cells/cmm and 1100 and 763 copies respectively and the groups were well-matched for race, HAART use and drug abuse (p>0.5 for all). LPS, CCL-2, IL-6 and sCD14 levels were not different in slope or quantity over time between LDP and NP. TNFRII levels were higher overall in progressors at T3 in unadjusted analysis (p=0.0005) and adjusted for HIVRNA (p=0.04) with a trend at T2 (p=0.01 unadjusted and 0.13 adjusted). SCD163 (figure) was significantly higher at T2 (p=0.007) and T3 (p<0.0001), (p=0.02 and <0.0001 respectively in the adjusted model) and for sCD163 the slope differed significantly between LDP and NP (p=0.02)



Conclusions: Soluble CD163 and TNFRII levels were significantly higher in liver disease progressors than non-progressors and the differences in these activation markers were apparent prior to the liver fibrosis outcome.

677 HIV/HCV Co-Infection Accelerated Liver Disease is Associated With Induction of M2-Like Macrophages

Moses T. Bility[1]; Feng Li[1]; Junichi Nunoya[1]; Guangming Li[1]; Eoin Feeney[2]; Raymond Chung[2]; Lishan Su[1]

[1]University of North Carolina, Chapel Hill, NC, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

Background: Chronic hepatitis B/C virus-induced liver diseases including fibrosis and cancer are exacerbated by human immunodeficiency virus (HIV) co-infection. Furthermore, HCV and HIV co-infection is a major cause of mortality in HIV-infected patients in western countries. The underlying pathogenic mechanisms by which chronic hepatitis viruses and HIV-1 co-infection induce and exacerbate liver diseases respectively remain unclear due to a lack of appropriate small animal models. Several studies show macrophages and other innate immune cells play a critical role in modulating host response and pathology; with M1 macrophages promoting pathogen clearance and immunity via secretion of Th1 associated cytokines, while M2-like macrophages impair Th1 immune response and promote tissue fibrosis and neoplasia via secretion of immunosuppressive cytokines.

Methods: We recently developed humanized mouse models, which carry both human immune system and human liver cells. The humanized mouse model is permissive for chronic hepatitis B/C virus and HIV infections. Briefly, to generate humanized mice, immunodeficient mice are transplanted with human fetal liver - derived hematopoietic stem cells and progenitor liver cells, followed by mouse hepatocyte depletion. Importantly, the humanized mouse model is the only *in vivo* model that support anti-viral human immune responses, and develops human immune cells mediated chronic liver inflammation, fibrosis and neoplasia in chronic hepatitis virus infections. HIV infection of humanized mice results in AIDS associated pathogenesis including CD4+ T cells depletion and hyper-immune activation. Additionally, preliminary results show HIV/HCV co-infection of humanized mice results in exacerbated liver pathogenesis. Lastly, we uterlized patient liver samples from mono-infected or co-infected HIV/HCV patients.

Results: Analysis of HCV-induced liver inflammation in both humanized mice and patient liver samples showed high levels of macrophages of predominately M2-like phenotypes localized to cirrhotic and neoplastic regions. Interestingly, chronic HIV infection is also associated with M2-like macrophage polarization in both humanized mice and patients. Importantly, HIV/HCV co-infection-induced accelerated liver disease was associated with increased M2-like macrophage activation.

Conclusions: Results from this study suggests a critical role for macrophage polarization in HIV/HCV-induced accelerated liver pathogenesis.

678 HIV Infection Is Associated With an Impaired Anti-HCV Activity of NK-Like T Cells

Pavlos Kokordelis[1]; Benjamin Krämer[1]; Christoph Boesecke[1]; Esther Voigt[2]; Patrick Ingiliz[3]; Andreas Glässner[1]; Franziska Wolter[1]; Ulrich Spengler[1]; Jürgen K. Rockstroh[1]; Jacob Nattermann[1]

[1]University of Bonn, Bonn, Germany; [2]Praxis am Ebertplatz, Cologne, Germany; [3]Medical Center for Infectious Diseases, Berlin, Germany

Background: Co-infection with the hepatitis C virus (HCV) is a major cause of morbidity and mortality in HIV(+) patients.

In HIV(-) patients CD3+CD56+ NK-like T cells, a subset of innate lymphocytes, have been suggested to modulate outcome of acute hepatitis C. However, it remained unclear whether these cells display direct anti-HCV activity and how HIV co-infection may modulate functions of CD3+CD56+ NK-like T cells.

Here, we show that CD3+CD56+ NK-like T cells can effectively block HCV replication but are functionally impaired in HIV(+) patients.

Methods: Eight HIV mono-infected patients, 12 HIV(+) patients with chronic hepatitis C, 8 HIV(-) patients with chronic HCV infection as well as 12 healthy individuals were enrolled into this study. Peripheral NKT cells (CD3+CD56+) were phenotypically analyzed by flow-cytometry. IFN-γ secretion and anti-HCV activity of NKT cells were analyzed using the HuH7 HCV replicon system.

Results: Un-stimulated CD3+CD56+ NK-like T cells from healthy donors only displayed a moderate anti-HCV function. However, stimulation with IL-12/IL-15 significantly increased the ability of CD3+CD56+ NK-like T cells to block HCV replication. Supernatants of IL-12/IL-15 stimulated CD3+CD56+ NK-like T cells also significantly inhibited HCV replication in vitro, suggesting that non-cytolytic mechanisms may play a major role. Accordingly, we only observed minimal killing of HuH7 HCV-replicon cells by CD3+CD56+ NK-like T cells. Moreover, we found stimulation with IL-12/IL-15 to significantly increase IFN-γ production and blocking of IFN-γ with a specific antibody significantly reduced the anti-viral activity of CD3+CD56+ NK-like T cells.

However, when CD3+CD56+ NK-like T cells from HIV(+) patients were studied we found HIV infection to be associated with a significantly impaired IFN-γ production, irrespective of HCV co-infection. Accordingly, CD3+CD56+ NK-like T cells from HIV(+) patients were significantly less effective in blocking HCV replication in vitro than cells from healthy individuals.

Phenotypic analysis revealed that HIV(+) patients displayed a significantly lower frequency of CD161+CD3+CD56+ NK-like T cells compared to controls. Of note, frequency of CD161-expressing cells was positively correlated with IFN-γ production.

Conclusions: Taken together, our data indicate that HIV infection is associated with an impaired anti-HCV activity of CD3+CD56+ NK-like T cells which might represent a novel mechanism of dysregulated immune response in HIV/HCV co-infected patients.

679 Dys-Regulated Cross Talk Between CD4+ T Cells and NK Cells in HIV/HCV Coinfection

Benjamin Krämer[1]; Andreas Glässner[1]; Claudia Zwank[1]; Felix Goeser[1]; Christoph Boesecke[1]; Patrick Ingiliz[2]; Christian P. Strassburg[1]; Ulrich Spengler[1]; Jürgen Rockstroh[1]; Jacob Nattermann[1]
[1]University of Bonn, Bonn, Germany; [2]Medical Center for Infectious Diseases, Berlin, Germany

Background: HCV/HIV co-infection is associated with an accelerated progression of liver disease as compared to HCV mono-infection. Natural killer cells are considered to play an important role in hepatits C. Increasing data indicate that CD4+ T cells critically modulate NK cell activity. Dys-regulation of the CD4+ T cell pool is a hallmark of HIV infection. Thus, we speculated that an altered cross-talk between CD4+ T cells and NK cells might be involved in the immunopathogenesis of HIV/HCV co-infection.

Methods: 40 HIV-infected patients, including 21 individuals that were HIV RNA(-)(<40 copies/ml) under HAART and 19 therapy-naïve HIV RNA(+) patients, as well as 20 healthy controls were enrolled into this study. CD3/CD28 stimulated CD4+ T cells were analysed for IL-2 secretion by flow cyotmetry. Antiviral activity of total PBMCs was studied using the HCV-replicon system. IFN-g secretion and anti-HCV activity of NK cells were analyzed in the presence/absence of CD4+ T cells.

Results: PBMCs from HIV(+) were significantly less effective in blocking HCV replication than cells from healthy controls ($p<0.001$). We also observed HIV infection to be associated with a significantly impaired IFN-g secretion of NK cells ($p<0.001$). Inhibition of HCV replication as well as IFN-g secretion of NK cells was positively correlated with CD4+ T cell counts in untreated HIV RNA(+) ($p<0.05$) but not in those under effective HAART. Moreover, we found viraemic HIV infection to be associated with reduced IL2 secretion of CD4+ T cells compared to healthy controls and HIV RNA(-). In line with previous results of our group we found activated CD4+ T cells to effectively stimulate IFN-g secretion of NK cell from healthy controls. Surprisingly, the ability of CD4+ T cells from healthy controls and HIV(+) to trigger activity of healthy NK cell did not differ significantly. However, when NK cells from HIV(+) were tested we found that neither autologous CD4+ T cells nor cells from healthys were able to trigger IFN-g secretion, indicating an NK cell intrinsic defect. Of note, this dys-regulated ability to respond to CD4+ T cell-mediated stimulation was also seen in HIV(+) patients under effective HAART.

Conclusions: Our findings indicate that HIV infection is associated with a dys-regulated cross-talk between CD4+ T cells and NK cells, resulting in an impaired anti-HCV NK cell activity which might represent a novel mechanism involved in accelerated progression of HCV-associated liver disease in HIV co-infected patients.

680 HIV/HCV Coinfection Is Associated With Significant Alterations of the NK Cell Pool

Dominik J. Kaczmarek[1]; Pavlos Kokordelis[1]; Benjamin Krämer[1]; Andreas Glässner[1]; Franziska Wolter[1]; Patrick Ingiliz[2]; Christian P. Strassburg[1]; Ulrich Spengler[1]; Jürgen Rockstroh[1]; Jacob Nattermann[1]
[1]University of Bonn, Bonn, Germany; [2]Medical Center for Infectious Diseases, Berlin, Germany

Background: Hepatitis C virus (HCV) co-infection in HIV(+) patients is associated with faster progression of liver disease as compared to HCV mono-infection. Natural killer (NK) cells critically modulate the natural course of hepatitis C. Of note, chronic infection with HCV as well as HIV mono-infection have been shown to be associated with significant alterations of the NK cell pool. However, little data is available concerning phenotype and function of NK cells in HIV/HCV infection.

Methods: A total of 22 HIV/HCV patients were enrolled into this study. As control 70 patients with chronic hepatitis C, 39 HIV mono-infected patients and 55 healthy individuals were analyzed. NK cell phenotype as well as IFN-γ production and degranulation of NK cells were studied by flow cytometry.

Results: Frequency of NK cells in HIV(+) patients was significantly lower than in healthy individuals ($p<0.01$) irrespective of HCV co-infection but did not differ significantly to that observed in HCV mono-infected patients.

Moreover, HIV/HCV co-infection was associated with significantly decreased expression of the NK maturation/differentiation markers CD27, CD127, CD62L and CD161 compared to healthy controls ($p<0.01$ for each comparison). Of note, expression of these markers in HIV(+)/HCV(+) also differed significantly from that observed in HCV mono-infected patients but was similar to HIV(+)/HCV(-) patients, indicating that these alterations were mainly attributable to HIV infection.

Similar observations were made regarding expression of C-type lectin NK cell receptors with low NKG2A but high NKG2C expression in HIV(+) patients, irrespective of HCV co-infection ($p<0.01$ vs. HCV or healthy).

In contrast, we found HIV/HCV co-infection to be associated with a significantly lower frequency of NKp30-expressing NK cells compared to both HCV and HIV mono-infected patients ($p<0.001$), suggesting a synergistic effect of both viruses.

More importantly, we found NK cells from co-infected patients to display highly dys-regulated functional activity with significantly lower IFN-γ production and degranulation than in healthy donors and HIV or HCV mono-infected patients (both $p<0.01$ for each comparison).

Conclusions: Our data indicate that HIV/HCV co-infection is associated with significant alterations of NK cell phenotype and functions, which might be involved in the rapid progression of liver disease observed in co-infected patients.

681 Dynamic Changes of CXCL10 Isoforms and DPP4 During IFN-Free Treatment for HCV

Eric G. Meissner[1]; Jeremie Decalf[2]; Armanda Casrouge[2]; Henry Masur[3]; Shyam Kottilil[4]; Darragh Duffy[2]; Matthew L. Albert[2]
[1]Medical University of South Carolina, Charleston, SC, US; [2]Institut Pasteur, Paris, France; [3]National Institutes of Health (NIH), Bethesda, MD, US; [4]University of Maryland School of Medicine, Baltimore, MD, US

Background: The intrahepatic endogenous interferon response fails to promote hepatitis C virus (HCV) clearance once chronic infection is established. The interferon (IFN)-stimulated chemokine CXCL10 (IP-10) is hepatically produced in chronic infection. A short CXCL10 isoform with antagonistic properties is generated by DPP4 activity, and likely contributes to impaired immunity in chronic HCV infection. We previously showed that IFN-free treatment of chronic HCV with sofosbuvir and ribavirin (SOF/RBV) is accompanied by rapid down-regulation of endogenous interferon activity. There was a trend towards higher pre-treatment CXCL10 levels in eventual relapsers ($p=0.12$, 994 pg/ml SVR ($n=28$), 1249 pg/ml relapsers ($n=14$)). Here, we examined how antagonistic, agonistic, and total CXCL10 levels and DPP4 activity changed during therapy, and whether they were associated with treatment outcome.

Methods: Serum was analyzed from patients who achieved SVR ($n=11$) or who relapsed ($n=10$) after treatment with 24 weeks of SOF/RBV on the NIH/NIAID SPARE trial (NCT01441180). Total, antagonistic, and agonistic CXCL10 was measured by Simoa (Quanterix) assay in triplicate at day 0, day 7, and week 20 of treatment. DPP4 levels were measured by ELISA and activity by DPP-Glo™ Protease assay (Promega). Data were analyzed by the Mann Whitney t-test or by Pearson correlation using Prism 6.0 software.

Results: In this cohort of patients, agonist ($p=0.038$) and total ($p=0.0079$) CXCL10 were significantly higher pre-treatment in patients who later relapsed, while the N-terminal truncated form of CXCL10 did not differ ($p=0.31$). All forms of CXCL10 decreased rapidly on treatment irrespective of treatment outcome. DPP4 activity correlated with pre-treatment levels of antagonistic CXCL10 ($p=0.0027$), but not agonistic or total CXCL10. Interestingly, there was no change in DPP4 activity or levels by week 1 of treatment, when all CXCL10 isoforms had declined, while activity had declined by week 20 of treatment. In patients who relapsed, CXCL10 concentration and DPP4 activity returned to pre-treatment levels.

Conclusions: Pre-treatment total and agonistic CXCL10, but not the antagonistic DPP4 cleavage product, were associated with treatment outcome in this subset of patients. The delayed kinetic decline of DPP4 activity relative to CXCL10 expression suggests the DPP4 pathway is not immediately regulated by endogenous interferon, providing insight into hepatic immune regulation during IFN-free HCV therapy.

682 Mx1 and OAS1-2 SNPs Are Related With Severity of Liver Disease in HIV/HCV Coinfection

Mónica García-Álvarez[1]; Juan Berenguer[2]; Daniel Pineda-Tenor[1]; Maria Ángeles Jiménez-Sousa[1]; María Guzmán-Fulgencio[1]; Ana Carrero[2]; Teresa Aldamiz-Echevarria[2]; Francisco Tejerina[2]; Cristina Diez[2]; Salvador Resino[1]

[1]Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain; [2]Hospital General Universitario Gregorio Marañón, Madrid, Spain

Background: The innate immune response against viruses induces production of interferon (IFN) type I (alpha, beta) and type III (gamma), which in turn induces the expression of genes encoding various proteins with antiviral activity, including the myxovirus resistance protein (Mx) and the family of 2′-5′-oligoadenylate synthetase (OAS) enzymes. These proteins have been linked to the progression of chronic hepatitis C. The aim of this study was to investigate the association of single nucleotide polymorphisms (SNPs) at *Mx1* and *OAS1-2* genes with the severity of liver disease in human immunodeficiency virus (HIV)/hepatitis C virus (HCV) coinfected patients.

Methods: A cross-sectional study was carried out in 219 HIV/HCV coinfected patients who had undergone liver biopsy. Genotyping of *Mx1* (rs464397, rs458582 and rs469390), *OAS1* rs2285934, and *OAS2* rs1293762 polymorphisms were performed by using GoldenGate® assay with VeraCode® technology. The outcome variables studied were: i) significant fibrosis (METAVIR F≥2); ii) moderate necroinflammatory activity grade (METAVIR A≥2). The genetic association study was carried out according to a dominant model of inheritance, which was the model that best fit to our data.

Results: Regarding *Mx1*, the presence of F≥2 was more frequent in patients with rs469390 AG/GG genotype (p=0.048). The presence of A≥2 was significantly more frequent in patients with rs469390 AG/GG (p=0.017) and rs464397 CT/CC (p=0.038) genotypes. Moreover, patients with rs469390 AG/GG and rs464397 CT/CC genotypes had higher likelihood of having A≥2 in liver biopsy (adjusted odds ratio (aOR)=0.48 (p=0.026) and aOR=0.45 (p=0.038), respectively).

Regarding *OAS1-2*, the presence of F≥2 was more frequent in patients with *OAS2* rs1293762 CC genotype (p=0.034). The presence of A≥2 was significantly more frequent in patients with *OAS1* rs2285934 CC genotype (p=0.038) and *OAS2* rs1293762 CC (p=0.008). However, we only found a significant association between *OAS2* rs1293762 CC genotype and the presence of A≥2 in liver biopsy (aOR=2.24, p=0.015).

Conclusions: Genetic polymorphisms of *Mx1* (rs464397 and rs469390), *OAS1* (rs2285934) and *OAS2* (rs1293762) were associated with higher severity of liver disease in HIV patients coinfected with HCV.

683 Treatment With DCV Plus ASV Reduces Immune Activation in HIV/HCV Coinfected Patients

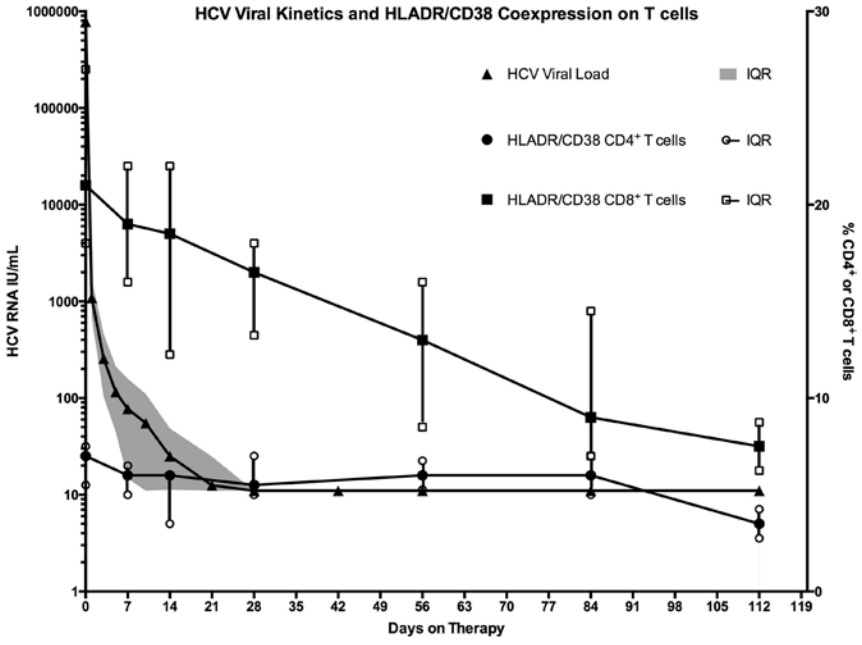
Eleanor M. Wilson[4]; Anita Kohli[3]; Julia B. Purdy[3]; Louisa Howard[1]; Sabrina Mangat[1]; Gebeyehu Teferi[2]; John Hogan[2]; Henry Masur[3]; Shyam Kottilil[1]

[1]National Institutes of Health (NIH), Bethesda, MD, US; [2]Unity Health Care, Washington, DC, US; [3]NIH, Bethesda, MD, US; [4]Leidos Biomedical Services, Inc, Bethesda, MD, US

Background: HIV/HCV co-infected subjects have higher levels of immune activation and are traditionally more difficult to treat with immune-based therapy for HCV compared to those with HCV mono-infection. Directly-acting antivirals have shown promising results in treating subjects with HCV mono-infection in the absence of interferon and ribavirin. Here we describe changes in immune activation associated with rapid decline in HCV RNA levels in HIV/HCV co-infected subjects receiving treatment for HCV with daclatasvir (DCV) and asunaprevir (ASV).

Methods: CONQUER is an ongoing prospective single center, phase 2 study conducted at the NIH Clinical Center of 30 HIV/HCV co-infected subjects with genotype 1 HCV, naïve to DAAs, on antiretroviral therapy with HIV viral load (VL) <50. Ten subjects with genotype 1b received DCV and ASV for 24 weeks; the next 20 genotype 1 subjects received DCV+ASV+BMS-791325 in a fixed-dose combination (FDC) for 12 weeks. HCV VL, measured using the Abbott assay, lower limit of quantification (LLOQ) 12 IU/ml; immune parameters, including $CD4^+$ T cell counts, HLA-DR/CD38 co-expression on $CD4^+$ and $CD8^+$ T cells; and liver function tests were followed prospectively. Median values and interquartile range (IQR) are reported; comparisons were made using Wilcoxon Rank tests.

Results: Subjects (n=10) were predominantly female (70%) and black (100%), with average age of 52 years and advanced liver disease (HAI fibrosis score <2, 40%); 20% were treatment-experienced, with previous pegylated interferon and ribavirin. HIV disease was well controlled, with HIV VL <50 on ART in 100% and average CD4 T-cell count of 855 cells/μL, and mean baseline HCV VL of 6.01 Log_{10} IU/mL. On therapy, HCV VL was below LLOQ in 30% by Week 2 and 89% by Week 4. After 2 weeks on therapy, CD4 remained unchanged (P>0.99), while co-expression of HLADR/CD38 declined by 14% and 28% respectively on $CD4^+$ (P=0.007) and $CD8^+$ T cells (P=0.017), and ALT, within the normal range at baseline, decreased by an average of 51% (P=0.004).



Conclusions: Virologically effective therapy with DCV plus ASV in HIV/HCV co-infected subjects is associated with a substantial decline in immune activation. The impact of this decline on non-AIDS defining morbidities in HIV infected subjects will need to be assessed in larger clinical studies.

684 Innate Immune Activation Pathways Overlap, Yet Are Distinct in HCV and HIV Infection

Lenche Kostadinova; Benigno Rodriguez; Donald Anthony
Case Western Reserve University, Cleveland, OH, US

Background: While chronic innate and adaptive immune activation are well recognized during HCV and HIV infection, drivers of this process are less clear, and whether the same drivers operate in each infection is unknown. Our data led us to sCD14 and LGALS3BP (90-kDa Mac-binding protein) as potential markers/mediators of immune activation in HCV-HIV infection.

Methods: We measured plasma sCD14, LGALS3BP, IL-6, LBP (LPS-binding protein) and IFABP (intestinal fatty acid binding protein) levels by ELISA in uninfected controls (n=12), HCV infected (n=30), HCV-HIV infected (n=30), and HIV infected (n=30) subjects not on therapy for HCV or HIV. HCV and HCV-HIV infected groups were stratified into low vs. hi APRI subgroups. HIV infected groups were evaluated again at 6 months on ART to determine the contribution of active HIV replication.

Results: In the absence of antiviral therapy HIV infection was associated with elevated plasma sCD14 ($p=0.025$), IL-6 ($p=0.010$), IFABP ($p=0.05$) and LGALS3BP ($p<0.0001$), while HCV infection was associated with elevated IL-6 ($p=0.022$) and LGALS3BP ($p<0.0001$). The latter remained significant in the hi-APRI subgroup for IL-6, and both hi and low APRI subgroups for LGALS3BP. Additionally, sCD14 ($p=0.019$) and IFABP ($p=0.05$) levels were greater in HCV hi APRI subjects than uninfected controls. Furthermore, both sCD14 ($p<0.0001$ and $p=0.025$) and LGALS3BP ($p=0.030$ and $p<0.0001$) levels were greater in HCV-HIV co-infected subjects than both HCV and HIV mono-infected subjects, consistent with contributions from each infection. Furthermore, while LBP was not significantly elevated in either HCV or HIV mono-infection, it was elevated during HCV-HIV co-infection ($p=0.005$). When evaluating relationships between each marker we observed that sCD14 levels positively correlated with LGALS3BP ($p=0.031$), IL-6 ($p= 0.05$) and LBP ($p=0.022$) during HCV infection, while sCD14 only correlated with LBP ($p=0.024$) during HIV infection. During HCV-HIV co-infection relationships between sCD14, LBP, and LGALS3BP were similar to those during HCV mono-infection. After initiation of ART for HIV infection, IL-6, LGALS3BP and LBP levels in HIV infected subjects normalized to those of uninfected controls, and those in HCV-HIV infected subjects declined to levels observed in HCV mono infected subjects.

Conclusions: Both HCV infection and consequent liver damage likely drive innate monocyte/macrophage activation by pathways that are overlapping but distinct from HIV infection.

685 A Novel Mechanism of Resistance to Multiple bNAbs Revealed by Natural Variation in Panel of 199 HCVpp

Ramy El-Diwany; Lisa Wasilewski; Madeleine Mankowski; Stuart C. Ray; Justin R. Bailey
Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: Broadly-neutralizing monoclonal antibodies (bNAbs) are informative for vaccine development for highly variable viruses including hepatitis C virus (HCV). However, HCV resistance to bNAbs is poorly understood, in part due to a lack of neutralization testing using diverse panels of HCV variants. HC33.4 and AR4A are two of the most potent bNAbs characterized to date, targeting the amino- and carboxy-terminus of HCV envelope (E2) respectively.

Methods: For each bNAb, we measured neutralization of a library of 199 genotype 1 HCV E1E2-pseudotyped particles (HCVpp). Using a novel R script, polymorphisms at each amino acid position in E1E2 were assessed for impact on neutralization resistance using Wilcoxon rank-sum test (corrected for multiple comparisons). Validation was performed using site directed mutagenesis in multiple E1E2 backgrounds. bNAb affinity for mutations in multiple E1E2 backgrounds was determined by ELISA.

Results: Multiple E1E2 clones with resistance to HC33.4 and/or AR4A were identified. Surprisingly, most resistance could not be attributed to amino acid changes in known mAb binding epitopes. Subtype 1a clones were more sensitive to mAb HC33.4 than subtype 1b clones ($P<1e-5$) and polymorphisms at positions 359, 403, 408, 414, 473, and 641 in subtype 1a clones were associated with resistance ($P_{corrected}<1e-5$ each), even though only 414 falls within the known binding epitope. Polymorphisms at 235, 293, 395, 403, and 655 were associated with AR4A resistance ($P_{corrected}<1e-5$ each), even though only 655 falls near AR4A's predicted binding epitope. Site directed mutagenesis of K408 to Methionine and L403 to Phenyalanine, in multiple E1E2 backgrounds conferred a 3.0-12.3-fold increase in resistance to HC33.4 ($P<0.01$). Interestingly, introduction of L403F also conferred 2.5-5.3-fold increase in resistance to AR4A ($P<0.01$ for each). Unlike previously characterized resistance polymorphisms, L403F did not reduce E1E2 binding affinity of either bNAb.

Conclusions: Our large diverse HCVpp panel in conjunction with a comprehensive computational pipeline allows for measurement of neutralizing antibody breadth, detection of differences in HCV subtype neutralization sensitivity, and identification of naturally occurring bNAb resistance polymorphisms in E1E2. A commonly occurring polymorphism at 403 confers resistance to two potent broadly neutralizing human mAbs targeting opposite ends of E2 without affecting binding affinity, suggesting a novel mechanism of neutralization resistance in HCV.

686 Single-Variant Sequencing Revealed Rapid HCV Evolution in HIV Immune Reconstitution

Lin Liu; David Nardo; Eric Li; Gary Wang
University of Florida, Gainesville, FL, US

Background: Human immunodeficiency virus (HIV) infection accelerates the progression of liver disease in Hepatitis C virus (HCV) co-infected individuals, raising the question of how immune status in co-infected individuals affects HCV quasispecies populations. We hypothesize that the structure and evolution of HCV populations in individuals with immune reconstitution differ from that in those with immune decline in HCV-HIV co-infections.

Methods: To precisely define and quantify individual HCV variants, we developed a single-variant sequencing (SVS) approach by combining random nucleotide tagging with an optimized Illumina MiSeq deep sequencing strategy. We applied this method to examine HCV quasispecies structure and evolution in envelope and NS3 genes in HCV-HIV co-infected subjects, and assess the abundance and dynamics of naturally occurring drug resistant mutations (DRMs) in NS3.

Results: We sequenced 35 serum samples collected across 10 years of follow-up from 6 HCV-HIV co-infected subjects. Three subjects who received ART early during follow-up experienced immune reconstitution. The other three subjects showed a gradual decline in CD4 count with delayed ART. A total of >16 million paired-end reads were generated to build 92,226 SVS consensus sequences based on unique sequence tags. Each consensus sequence represents an individual HCV variant. We showed that the SVS approach (1) corrected PCR/sequencing errors as well as resampling and amplification bias from PCR, and (2) provided an accurate representation of HCV population structure *in vivo*. Rapid non-synonymous sequence evolution was observed in hypervariable region 1 (HVR1) of E2, but not NS3, in subjects with immune reconstitution compared to subjects with immune decline. Notably, using SVS consensus, a naturally occurring DRM in NS3, aaVI170T, was detected as a minor variant (<1%) in 4 of 6 subjects over multiple visits. In contrast, an even distribution of minor DRMs across all DRM sites was observed based on raw reads ($P<10^{-32}$).

Conclusions: Single-Variant Sequencing accurately defines HCV quasispecies population structure and evolution *in vivo*. Immune reconstitution in HIV/HCV co-infection is associated with rapid sequence evolution in the envelope but not NS3, likely driven by increased immune pressure from enhanced humoral responses during antiretroviral therapy. Drug resistant mutations in NS3 can occur naturally at low frequencies in HCV-HIV co-infected individuals, which can be accurately identified and quantified using SVS.

THURSDAY, FEBRUARY 26, 2015

Session P-N8 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HCV Therapeutics: Preclinical Observations and Clinical Trials of DAAs

687 UNITY-1: Daclatasvir/Asunaprevir/Beclabuvir for HCV Genotype 1 Without Cirrhosis

Fred Poordad[1], William Sievert[2], Norbert Brau[3], **Samuel Lee**[4], Jean-Pierre Bronowicki[5], Ira Jacobson[6], Eric Hughes[7], Eugene Swenson[8], Philip Yin[8]
On behalf of the UNITY-1 Study Team

[1]Texas Liver Institute, San Antonio, Texas, United States; [2]Monash Health and Monash University, Melbourne, Victoria, Australia; [3]Bronx Veterans Affairs Medical Center, New York, New York, United States; [4]University of Calgary, Alberta Health Services, Calgary, Alberta, Canada; [5]Centre Hospitalier Universitaire de Nancy, Universite de Lorraine, Vandoeuvre les Nancy, France; [6]Weill Cornell Medical College, New York, New York, United States; [7]Bristol-Myers Squibb Co, Princeton, New Jersey, United States; [8]Bristol-Myers Squibb Co, Wallingford, Connecticut, United States

Background: The all-oral combination of daclatasvir (DCV; pangenotypic NS5A inhibitor), asunaprevir (ASV; NS3 protease inhibitor), and beclabuvir (BCV; non-nucleoside NS5B inhibitor) achieved high rates of SVR12 in a phase 2 clinical trial. This regimen, in a twice-daily fixed-dose combination tablet—DCV-TRIO regimen—was evaluated without ribavirin in HCV genotype (GT) 1-infected treatment-naive and -experienced patients without cirrhosis in a phase 3, open-label, international clinical trial.

Methods: All patients received 12 weeks of treatment with the fixed-dose combination of DCV 30 mg, ASV 200 mg, and BCV 75 mg twice daily. Key efficacy outcomes were SVR12 rates in the treatment-naive and -experienced cohorts, assessed separately.

Results: Baseline characteristics in the treatment-naive (N=312) and treatment-experienced (N=103) cohorts were comparable. Overall, patients were 58% male and 26% IL28B (rs1297860) CC genotype; 73% were infected with GT 1a and 27% with GT 1b. SVR12 was achieved by 92% and 89% of treatment-naive and –experienced patients, respectively. 17 patients with GT1b infection had NS5A resistance-associated variants (RAVs) at baseline; all 17 achieved SVR12. 25 of the 34 GT1a-infected patients with baseline NS5A RAVs achieved SVR12. Overall, 34 (8%) patients experienced virologic failure, including 21 with posttreatment relapse and 13 with on-treatment virologic failure. Among patients with GT1a infection who experienced failure, RAVs at positions NS5A-Q30, NS3-R155 and/or NS5B-P495 were the most frequently observed variants. One death occurred posttreatment and was considered not related to study treatment. There were 7 serious adverse events, all unrelated, and 3 (<1%) adverse events leading to treatment discontinuation. Adverse events (any grade) that were observed in >10% of patients included headache, fatigue, diarrhea, and nausea.

Conclusions: Twelve weeks of all-oral treatment with the fixed-dose combination of DCV, ASV, and BCV achieved high SVR12 rates in 415 patients with chronic HCV GT 1 infection without cirrhosis, confirming the potent antiviral activity of the DCV-TRIO regimen. DCV-TRIO demonstrated a favorable safety and tolerability profile in both treatment-naive and treatment experienced patients.

688 UNITY-2: Daclatasvir/Asunaprevir/Beclabuvir ± RBV for HCV Genotype 1 With Cirrhosis

Andrew Muir[1], Fred Poordad[2], Jay Lalezari[3], Gregory Dore[4], Christophe Hezode[5], Alnoor Ramji[6], Eric Hughes[7], **Eugene Swenson**[8], Philip Yin[8]
On behalf of the UNITY-2 Study Team

[1]Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina, United States; [2]Texas Liver Institute, University of Texas Health Science, San Antonio, Texas, United States; [3]Quest Clinical Research, San Francisco, California, United States; [4]Kirby Institute, University of New South Wales Australia, Sydney, New South Wales, Australia; [5]Hópital Henri Mondor, Université Paris-Est, Créteil, France; [6]University of British Columbia, Vancouver, British Columbia, Canada; [7]Bristol-Myers Squibb Co, Princeton, New Jersey, United States; [8]Bristol-Myers Squibb Co, Wallingford, Connecticut, United States

Background: The presence of cirrhosis in patients with chronic HCV infection can reduce response to HCV therapies; potent and well tolerated oral regimens are needed. The all-oral DCV-TRIO regimen includes daclatasvir (DCV; pangenotypic NS5A inhibitor), asunaprevir (ASV; NS3 protease inhibitor), and beclabuvir (BCV; non-nucleoside NS5B inhibitor) in a fixed-dose combination (FDC). We evaluated this regimen, with and without ribavirin (RBV), in treatment-naive and -experienced patients with HCV genotype (GT) 1 infection and compensated cirrhosis in a randomized, phase 3 clinical trial.

Methods: Patients were randomly assigned to receive a twice-daily FDC of DCV 30 mg, ASV 200 mg, and BCV 75 mg, with blinded RBV or placebo, for 12 weeks. SVR12 rates in the treatment-naive and experienced cohorts were evaluated separately as key efficacy outcomes. .

Results: Baseline characteristics were comparable between treatment-naive (N=112) and treatment-experienced (N=90) patients. Overall, patients were 66% male and 27% IL28B (rs1297860) CC genotype; 74% of patients had GT1a infection and 26% had GT1b. SVR12 was achieved by 98% and 93% of treatment-naive patients treated with DCV-TRIO + RBV and DCV-TRIO, respectively. Corresponding SVR12 rates for the experienced cohort were 93% and 87%. The presence of NS5A or NS3 polymorphisms at baseline did not appear to impact SVR12. Virologic failure was observed in 13 (6%) patients, including posttreatment relapse (10/13) and on-treatment failure (3/13). Ten of 13 patients with virologic failure had both NS5A and NS3 resistance variants at failure. Three serious adverse events (SAEs) were considered related to treatment, and there was 1 DCV-TRIO discontinuation due to adverse events. There were no deaths. Adverse events reported in >10% of patients included fatigue, headache, nausea, diarrhea, insomnia and pruritus. Reduction of hemoglobin to <9 g/dL during treatment was reported in 5% of patients who received RBV-containing therapy but in none of the patients receiving DCV-TRIO alone.

Conclusions: The all-oral fixed dose combination of DCV, ASV, and BCV, with or without ribavirin, achieved high rates of SVR12 after 12 weeks of therapy in patients with GT1 infection and compensated cirrhosis. The DCV-TRIO regimen with or without RBV was well tolerated.

689 Utility of Hepatitis C Viral-Load Monitoring With Ledipasvir and Sofosbuvir Therapy

Sreetha Sidharthan[2]; Anita Kohli[3]; Anu Osinusi[2]; Amy Nelson[1]; Zayani Sims[2]; Kerry S. Townsend[4]; Lydia Tang[1]; Michael Polis[4]; Henry Masur[2]; Shyam Kottilil[1]

[1]Institute of Human Virology, University of Maryland, Baltimore, MD, US; [2]NIH Clinical Center, Bethesda, MD, US; [3]Leidos Biomedical Research, Inc., Frederick, MD, US; [4]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

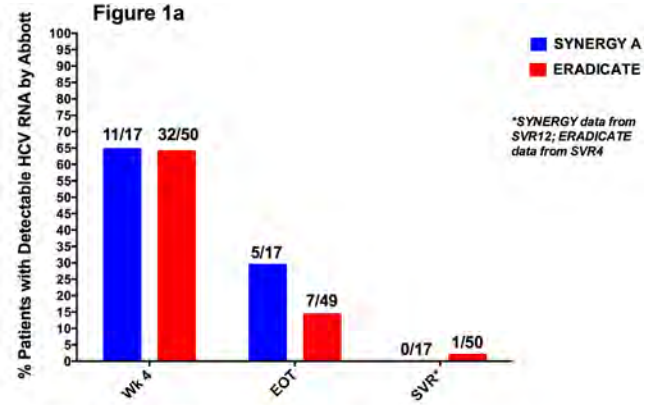
Background: Directly acting antivirals (DAA) are replacing interferon-based hepatitis C therapy. On interferon-based treatment, HCV RNA plasma levels were early predictors of treatment response and mainstays for response-guided therapy. However, the clinical utility of HCV RNA levels to guide duration of DAA therapy has not yet been determined. The aim of this study was to determine the ability of on-treatment plasma HCV RNA levels to predict treatment outcome in HCV mono-infected and HIV/HCV co-infected patients treated with ledipasvir and sofosbuvir.

Methods: In two NIAID clinical trials, SYNERGY A (HCV mono-infected, n=17) and ERADICATE (HIV/HCV co-infected, ARV naïve n=13, on cART n=37), subjects were treated with a fixed dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) for 12 weeks. In both trials, patients were treatment-naïve, non-cirrhotics, and infected with HCV genotype 1. Serial measurements of plasma HCV RNA were performed by the Roche COBAS TaqMan HCV test v1.0 and the Abbott real-time PCR assay. The positive predictive value and negative predictive value at week 4 and end of treatment (EOT) for both assays were calculated.

Results: By the Abbott assay on SYNERGY, 11/17 patients had detectable (6/17 quantifiable) HCV RNA at week 4 and 5/17 patients had detectable but unquantifiable HCV RNA at EOT (Figure 1a). All patients with undetectable HCV RNA at week 4 and EOT achieved SVR12, and none with detectable HCV RNA relapsed (PPV 100 and NPV 0). By the Roche assay (Figure 1b), all patients had undetectable HCV RNA at EOT and achieved SVR 12 (PPV 100).

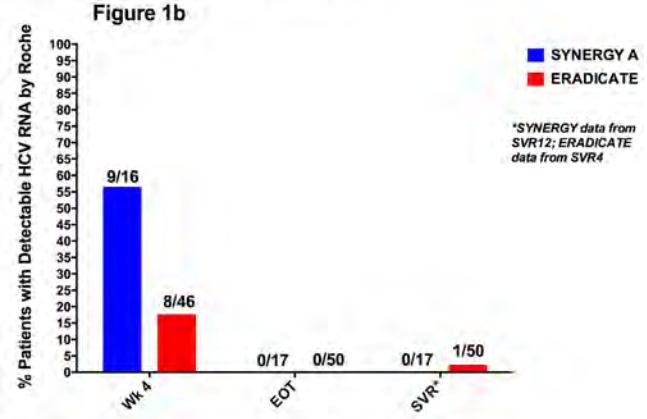
On ERADICATE, 32/50 patients had detectable (9/50 quantifiable) HCV RNA by the Abbott assay at week 4 (Figure 1a), 31 of whom achieved SVR4 (PPV 100 and NPV 3.1). At EOT, 7/49 patients had detectable but unquantifiable HCV RNA by the Abbott assay, all of whom achieved SVR4 (PPV 100 and NPV 0). By the Roche assay (Figure 1b), all 50 patients were undetectable at EOT and 1 relapsed (PPV 98).

Figure 1a



PPV (%)	100	100	100	100
NPV (%)	0	3.1	0	0

Figure 1b



PPV (%)	100	100	100	98
NPV (%)	0	12.5	N/A	N/A

Conclusions: Contrary to past experience with interferon-containing treatments, the presence of detectable HCV RNA levels at EOT is not predictive of relapse in these studies. The low negative predictive values at week 4 underscore the importance of continued therapy for patients who fail to achieve undetectable levels of HCV RNA early on during treatment because their chances of achieving SVR are still high.

690 Viral Kinetic Profiles of HCV Response to Telaprevir-Based Therapy in Patients With Hemophilia

Kenneth E. Sherman[1]; Ruian Ke[2]; Susan D. Rouster[1]; Alan S. Perelson[2]

[1]*University of Cincinnati, Cincinnati, OH, US;* [2]*Los Alamos National Laboratory, Los Alamos, NM, US*

Background: The majority of patients with inherited bleeding disorders who received blood-derived factor concentrates were infected with HCV with repeated exposures to multiple HCV species. It is hypothesized that wide quasispecies representation could affect treatment responses, and that lead-in might mitigate emergent viral breakthrough. The utility of lead-in vs. DAA-based therapy in hemophiliacs was evaluated using viral dynamic modeling methods.

Methods: Treatment-experienced subjects with hemophilia were treated with telaprevir/pegylated interferon alfa/weight-based ribavirin (T/P/R) and randomized to triple-drug start vs. lead-in for 1 month with P/R only. Intensive sampling of blood was performed at baseline, 3, 6, 12, 24, 48 and 72 hours after dosing, and again at days 7 and 10. Lead-in subjects underwent intensive sampling after addition of telaprevir (Week 5). Viral dynamic models were utilized for data analysis and treatment responses were assessed. Safety parameters studied included development of inhibitors to factor concentrates.

Results: Seven patients with hemophilia provided informed consent. Two were screen failures (spontaneous clearance/loss to f/u prior to drug start). Among the five treated subjects, all were male, 80% were Caucasian and 1 (20%) was black, non-Hispanic. Four subjects were IL28B genotype CT, and one was CC. The mean baseline HCV RNA titer was log 6.7 IU/ml. Three subjects were randomized to lead-in followed by addition of T after four weeks, and two received standard T/P/R therapy. The lead-in subjects' mean HCV RNA titer prior to beginning telaprevir (week 5) was 4.97. The efficacy parameter () for lead-in ranged from 0 to 0.9745 (mean= 0.514). Addition of telaprevir resulted in a mean efficacy of more than 0.999. This was comparable to subjects who started all three medications simultaneously. Overall efficacy in those with hemophilia was higher than historical non-hemophilia controls not treated with ribavirin (data not shown). Ultimately, 4/5 subjects (80%) achieved SVR. Adverse event profiles were similar to that observed in non-hemophilia cohorts. There was no evidence of factor inhibitor formation.

Conclusions: T/P/R was highly effective in HCV clearance among hemophilic subjects. There was no evidence that lead-in provided benefit in terms of response efficacy, but addition of telaprevir led to rapid viral decline. These data support DAA-based therapy in those with inherited bleeding disorders.

691 Hematologic Analysis of ABT-450/r/Ombitasvir and Dasabuvir + RBV in TURQUOISE-I

Robert S. Brown[1]; David Wyles[2]; Jihad Slim[3]; Peter J. Ruane[4]; Barbara McGovern[5]; Roger Trinh[5]; Yiran Hu[5]; Joseph J. Eron[6]

[1]Johns Hopkins University, Baltimore, MD, US; [2]University of California San Diego, La Jolla, CA, US; [3]St Michael's Medical Center, Newark, NJ, US; [4]Peter J. Ruane MD Inc, Los Angeles, CA, US; [5]AbbVie, Inc, North Chicago, IL, US; [6]University of North Carolina, Chapel Hill, NC, US

Background: Combination therapy of ribavirin (RBV)+peginterferon (pegIFN) with protease inhibitors for the treatment of HCV is commonly associated with hematologic abnormalities. We sought to analyze immune parameters in patients co-infected with HCV and HIV-1 treated with the 3 direct-acting antiviral (3D) regimen of co-formulated ABT-450 (identified by AbbVie and Enanta)/ritonavir/ombitasvir and dasabuvir given with weight-based RBV. SVR_4 rates of 93.5 and 96.9% were observed with 12- and 24-weeks of 3D+RBV therapy in patients co-infected with HCV/HIV-1.

Methods: TURQUOISE-I is a 2-part ongoing, randomized, open-label Phase 2/3 study evaluating the safety and efficacy of 3D+RBV for 12- or 24-weeks in HCV genotype 1/ HIV-1 co-infected treatment-naïve or pegIFN/RBV -experienced adults with and without cirrhosis. Laboratory values were assessed at every study visit and post-treatment visit. Treatment-emergent adverse events (AEs) were assessed from the first dose until 30 days after the last dose for any patient who received at least one dose of study drugs.

Results: Hemoglobin decreases were comparable between 12- and 24-week treatment arms (Table). Treatment-emergent anemia was reported in 1 patient in the 12-week arm and in 3 patients in the 24-week arm. RBV dose modification due to decreased hemoglobin occurred in 6 patients (4 in the 12-week arm; 2 in the 24-week arm); all achieved SVR_{12}. No patient had a post-baseline Grade 3 or 4 decrease in hemoglobin. No patient used erythropoietin or received a blood transfusion. Mean absolute CD4+ T cell counts and lymphocytes decreased during treatment and increased to above baseline levels by post-treatment week 12 (Table). CD4 percentages remained stable over time in both treatment arms. No patient had clinically significant abnormalities in platelet or white blood cell counts. Among the 3 patients who experienced a CD4+ T cell count <200 cells/mm^3 or CD4+ percentage <14% during treatment, none experienced an AIDS-associated opportunistic infection.

Hemoglobin decrease, n (%)	3D +RBV 12 weeks N=31	3D+RBV 24 weeks N=32
Grade 1 (LLN to 10 g/dL)	14 (45.2)	18 (56.3)
Grade 2 (≤10 to 8 g/dL)	4 (12.9)	3 (9.4)
Grade 3 (≤8 to 6.5 g/dL)	0	0
Grade 4 (<6.5 g/dL)	0	0
Total lymphocytes, mean absolute count , x10^9/L		
BL	1.88	1.96
Week 4	1.74	1.93
Week 12	1.52	1.62
PTW12	2.01	2.11
CD4+ T cells, mean absolute count, /(MCL) and percentage (%)		
BL	633.3 (31.2)	625.3 (29.2)
Week 4	602.6 (31.5)	618.4 (29.4)
Week 12	516.0 (33.0)	515.8 (30.7)
PTW12	677.7 (31.4)	645.8 (29.9)

LLN: lower limit of normal; PTW: post-treatment week

Conclusions: Among HCV/HIV-1 co-infected treatment-naïve and -experienced patients, anemia events were infrequent with 3D+RBV treatment and did not affect treatment outcomes. Transient declines in absolute CD4+ T cells paralleled changes in total lymphocyte count, which is consistent with known hematologic effects of RBV.

692 Effect of HIV Coinfection on Adherence to a 12-Week Regimen of HCV Therapy With Ledipasvir/Sofosbuvir

Kerry S. Townsend[1]; Tess L. Petersen[2]; Lori A. Gordon[2]; Amy Nelson[1]; Cassie Seamon[2]; Chloe Gross[3]; Anu Osinusi[2]; Michael A. Polis[1]; Henry Masur[2]; Shyam Kottilil[1]

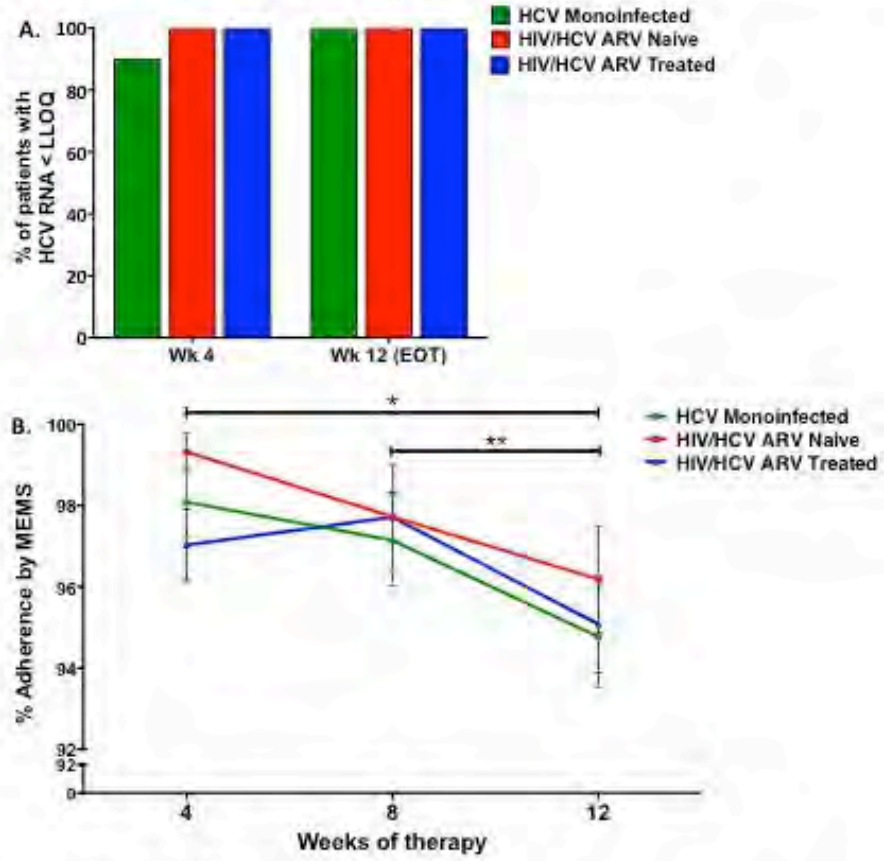
[1]National Institute of Allergy and Infectious Diseases, Bethesda, MD, US; [2]National Institutes of Health, Bethesda, MD, US; [3]Leidos Biomedical 18 Research Inc, Frederick, MD, US

Background: The treatment of hepatitis C virus (HCV) infection is rapidly evolving to interferon (IFN) and ribavirin (RBV) free treatment with directly acting antiviral agents (DAAs). The impact of DAAs on HCV treatment adherence in HIV/HCV co-infected populations has not been extensively evaluated. We compared adherence rates of the IFN and RBV free DAA regimen of ledipasvir/sofosbuvir (LDV/SOF) between HCV mono-infected and HIV/HCV co-infected patients.

Methods: Participants were representative of the urban Washington D.C. cohort and were HCV treatment naïve, genotype 1 study subjects from two National Institute of Allergy & Infectious Diseases (NIAID) phase 2 clinical trials (Synergy A: HCV mono-infected participants, n=20, and Eradicate: HIV/HCV co-infected participants, antiretroviral (ARV) naïve, n=13, on combination ARV therapy, n=37). Patients were treated with LDV (90 mg) + SOF (400 mg) as a fixed dose combination once daily for twelve weeks. Adherence was measured using three tools: MEMS (Medication Event Monitoring System) caps, pill counts, and patient report. Adherence over time was compared using Wilcoxon T test. Analyses were performed using PRISM 6.0 (Graphpad).

Results: Patients enrolled were predominately African American (83%) and male (73%), with a median age of 59 years. Patients in all three-treatment groups had prompt viral load decline associated with high adherence rates. Only twelve out of the sixty patients (20%) missed 4 or more pills. However, patient adherence significantly decreased from baseline - week 4 compared to week 8 - 12 in all three groups [HCV mono-infected (p=0.02), HIV/HCV ARV naive (p=0.01), and HIV/HCV ARV treated patients (p=0.01)].

Figure 1. Treatment Response Rates and Adherence Rates during Treatment
(A) Percent of patients below lower limit of quantification (<43 IU/ml by Roche Assay).
(B) Adherence over the course of treatment as measured by MEMS.



Mean percent adherence with SEM.
Adherence is measured here from baseline to four weeks, four weeks to eight weeks, and eight weeks to end of treatment (12 weeks).
*Percent Adherence was significantly different in all three groups from week 4 to week 12: HCV Monoinfected (p=0.02), HIV/HCV ARV Naïve (p=0.01), HIV/HCV ARV Treated (p=0.01).
**Percent Adherence was significantly different between week 8 and week 12 for HIV/HCV ARV Treated patients (p=0.009)

Conclusions: Adherence to the single daily tablet of LDV/SOF in this urban population was high and coupled with complete HCV viral suppression. However, adherence significantly declined over the course of treatment, suggesting that shorter duration DAA therapies should be evaluated for HCV treatment efficacy in this patient population.

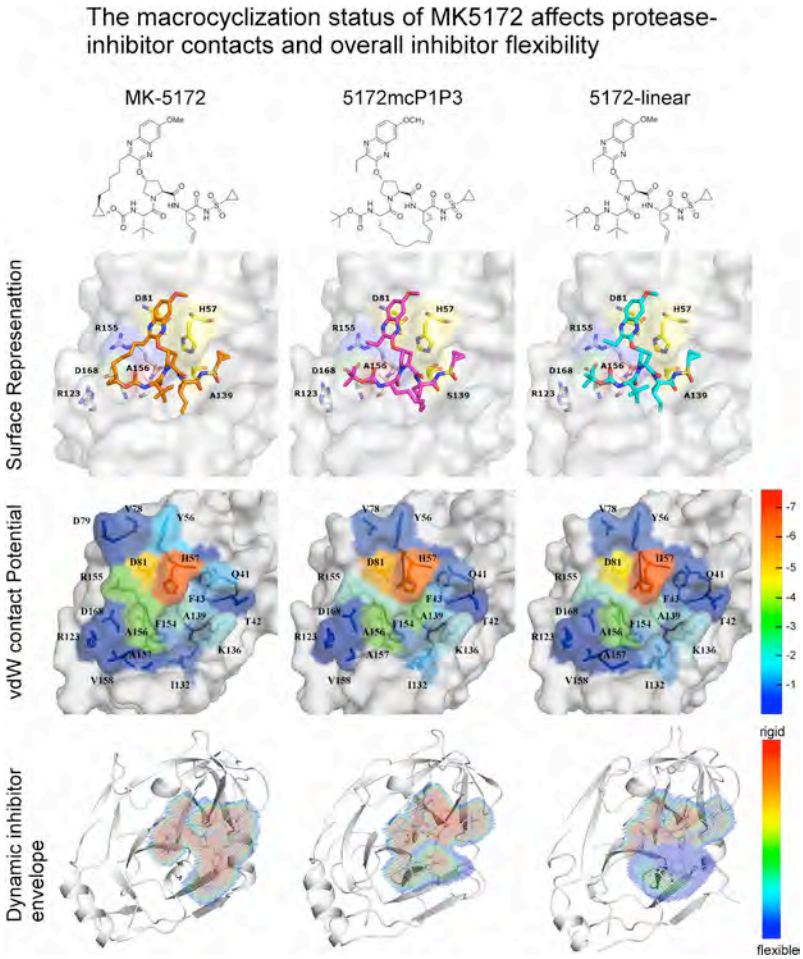
693 Investigation of the Role of Macrocyclization in HCV Protease Inhibitor MK-5172

Djadé I. Soumana; Kristina Prachanronarong; Nese Kurt Yilmaz; Ali Akbar; Cihan Aydin; Celia A. Schiffer
University of Massachusetts Medical School, Worcester, MA, US

Background: Structure guided drug design has been a powerful tool for the discovery and development of inhibitors to the viral HCV NS3/4A protease. The NS3/4A protease inhibitors (PIs) have benefited from extensive optimizations in the common P4 capping, P3-P1' peptidomimetic scaffold and various macrocyclization states. However, neither structural nor thermodynamic information have been presented evaluating the benefits of different protease macrocyclization states in the context of resistance. MK-5172 is extremely potent against the wildtype (WT) enzyme, while subverting resistance to R155K and D168A due to packing against the protease catalytic triad, this inhibitor is susceptible to A156T due to a strong steric clash

Methods: A combination of standard protein crystallographic, molecular dynamic, kinetic and thermodynamics methods were applied to the protease domain of HCV NS3/4A WT and A156T resistance variant. Detailed structural analysis, including fit within the substrate envelope and dynamic inhibitor envelope, was applied to a series of MK-5172 macrocyclic analogs and compared to the parent MK5172. This data was compared with the thermodynamics of inhibitor binding.

Results: A crystallographic, biochemical and thermodynamic characterization of the role of macrocyclization in drug resistance will be presented for the HCV NS3/4A PI MK-5172 and a series of analogs. Through a series of crystal structures in complex with WT and A156T HCV protease variants compared with thermodynamic data we provide atomic level insight into the inhibitor's unique binding mode and how the macrocyclization impacts susceptibility to drug resistance



Conclusions: Through leveraging evolutionarily restricted regions in the HCV protease robust inhibitors can be designed to increase the barrier to resistance

THURSDAY, FEBRUARY 26, 2015

Session P-N9 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Mental Health and Treatment Adherence with Direct-Acting Antivirals

694 Impact of Baseline Mental Health on Adherence to Interferon-Free HCV Therapy

Jack Masur[1]; Lydia Tang[1]; Amy Nelson[1]; Anu Osinusi[1]; Anita Kohli[2]; Rachel Silk[2]; Chloe Gross[2]; Sarah Kattakuzhy[2]; Michael Polis[3]; Shyam Kottilil[1]

[1]University of Maryland, Baltimore, MD, US; [2]National Institutes of Health, Bethesda, MD, US; [3]National Institutes of Health, Bethesda, MD, US

Background: Mental health disorders (MHD) have long presented a barrier to treatment for individuals with chronic hepatitis C (HCV) infections. The complexity and side effect profile of interferon based therapies make many patients with MHD ineligible or unwilling to be treated. Directly acting antiviral therapy is replacing interferon based HCV therapy. This study aims to determine the impact of baseline MHD on adherence and effectiveness of the IFN and RBV free regimen ledipsavir/sofosbuvir (LDV/SOF) in HIV negative and positive hepatitis C patients.

Methods: Two NIAID clinical trials, SYNERGY A (HCV mono-infected, n=20) and ERADICATE (HIV/HCV co-infected; ARV naïve n=13, on cART n=37), treated HCV genotype-1, treatment naïve study subjects with a fixed dose combination of ledipsavir (90mg) and sofosbuvir (400mg) daily for 12 weeks. We identified all participants with a baseline MHD defined as a major DSM-IV diagnosis such as major depression, bipolar disorder, schizophrenia, generalized anxiety, post-traumatic stress disorder (PTSD), and depression with anxiety or those requiring anti-depressants, antipsychotics, mood stabilizers or psychotropics. Adherence was measured using medication event monitoring systems (MEMS) caps. Serial measurements of plasma HCV RNA levels were performed using the Roche RealTime HCV RNA assay.

Results: Of 20 participants in SYNERGY A, 7 (40%) met the criteria for significant baseline MHD. The prevalence of disorders was as follows: depression (15%), depression with anxiety (15%), bipolar disorder (5%), PTSD (5%), and schizophrenia (5%). Of 50 participants in ERADICATE, 15 (30%) met the criteria for significant baseline MHD. The prevalence of disorders was as follows: depression (16%), bipolar disorder (10%), PTSD (6%), and anxiety (2%). There was no significant difference in adherence to MEMS between MHD patients and non-MHD patients in either study (96% vs. 97% for SYNERGY and 97% vs. 97% for ERADICATE, p.0.05 for both) (Figure 1a, p>0.05). There was no significant difference between MHD patients and non-MHD patients who achieved SVR12 for SYNERGY and SVR4 for ERADICATE (100% vs. 100% for SYNERGY and 100% vs. 97% for ERADICATE, p>0.05 for both) (Figure 1b).

Figure 1a

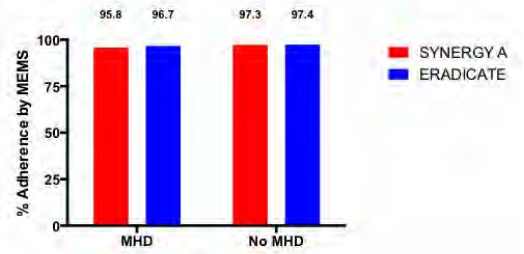
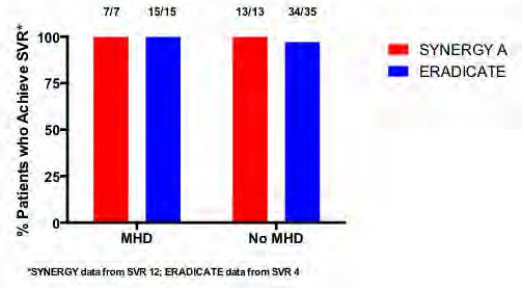


Figure 1b



Conclusions: Since 31% of our study subjects had serious, controlled MHD when starting therapy, it appears that controlled major psychiatric disorders may be no barrier to the successful completion of anti-HCV therapy using a newer DAA combination.

695 Mental Health Impact of HCV Treatment in HIV/HCV Patients: DAA vs IFN-Based Therapy

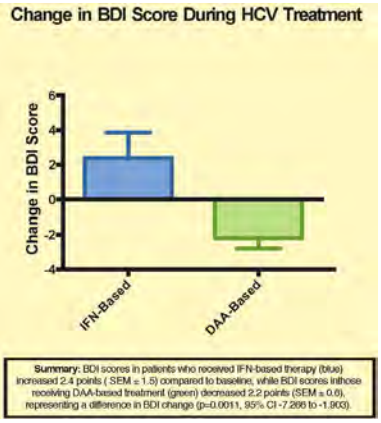
Louise Lundgren[1]; Sarah Kattakuzhy[2]; Angie Price[2]; Catherine Seamon[3]; Amy Nelson[4]; Anita Kohli[2]; Rachel Silk[2]; Chloe Gross[2]; Henry Masur[1]; Shyamasundaran Kottilil[4]

[1]National Institutes of Health Clinical Center, Bethesda, MD, US; [2]Leidos Biomedical Research, Inc, Frederick, MD, US; [3]Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, US; [4]Institute of Human Virology, University of Maryland, Baltimore, MD, US

Background: Depression is one of the most important complications of IFN-based chronic hepatitis C treatment, affecting one in four patients. Psychiatric side effects of IFN have significant clinical implications, creating a relative contraindication to IFN in those with mental dissorders. Patients with HIV/HCV-coinfection are particularly vulnerable given the prevalence of psychiatric comorbidities and higher adverse event rates to IFN containing therapy. In phase III studies of HCV treatment utilizing directly acting antivirals (DAA), psychiatric side effects outside of insomnia have not been described. The current analysis seeks to evaluate treatment-induced depression as a complication of HCV therapy in both DAA- and IFN-based regimens.

Methods: Beck's Depression Inventory (BDI) scores from three phase II clinical trials for treatment of HCV in HIV/HCV coinfected patients were retrospectively analyzed. 26 patients were included who were treated with peg-IFN and ribavirin for 48 weeks, while 50 patients were included who were treated with 12 weeks of sofosbuvir/ledipasvir. BDI scores were collected at pre-treatment day 0, during treatment and 1 to 8 weeks post-treatment.

Results: Average BDI-scores at day 0 were similar between IFN-based (6.96) and DAA-based (5.38) treatment groups (p=0.34). During IFN treatment, BDI scores rose an average of 2.4 points, while scores declined an average of -2.2 points for patients on DAAs (p=0.001, 95% CI:-7.3 to -1.9). Mean mid-treatment scores varied significantly between IFN and DAA-based therapy, with scores of 9.35 (corresponding to mild-moderate depression) and 3.18 respectively (p=0.001, 95% CI:-9.8 to -2.5). Post treatment, BDI scores in DAA treated patients were significantly lower as compared to patients who received IFN based treatment (p=0.02, 95% CI:-6.4 to -0.5). While post IFN containing treatment BDI scores returned to baseline, scores were significantly lower post DAA treatment compared to pre-therapy(p=.0008, 95% CI:-3.9 to -1.1).



Change in BDI Score During HCV Treatment

Conclusions: DAA-based therapy is not complicated by depression while on treatment, and may be the optimal choice for patients with psychiatric comorbidities. The mechanism of BDI score decline in DAA-treated patients post-treatment is unclear. However, given the known improvement in HCV neurocognitive dysfunction after SVR, it is plausible that this result is mediated by the rapid virologic response associated with DAA-based therapy, rather than medication effect, and is likely to be addressed in larger clinical trials.

THURSDAY, FEBRUARY 26, 2015

Session P-N10 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HCV: Resistance to Antiviral Agents

696 Characterization of Naturally Occurring Resistance to HCV NS5A Inhibitors

Jennifer Cook; Owen Solberg; Alicia Newton; Suqin Cai; Arne Frantzell; Jacqueline Reeves; Christos J Petropoulos; Jonathan Toma; **Wei Huang**

Monogram Biosciences, South San Francisco, CA, US

Background: Clinical trials with some NS5A inhibitor-containing regimens have resulted in less favorable responses among individuals with GT1a compared to GT1b HCV. To assess whether quantitative or qualitative differences in naturally occurring resistant variants may explain the discordant response rates, we used deep sequencing and recombinant replicons to determine the prevalence and resistance profiles of NS5A inhibitor resistant variants in HCV from DAA treatment-naïve individuals.

Methods: NS5A regions were amplified from 109 plasma samples (1a=71, 1b=38) and incorporated into a Con1 luciferase reporter replicon. NS5A sequencing was performed using the Illumina MiSeq platform. NS5A inhibitor resistance-associated variants (RAVs) located at positions 28, 30, 31, 32, and 93 were recorded (lower threshold=0.5%). RAVs were introduced into reference replicons by site-directed mutagenesis (SDM). Replicons containing plasma-derived NS5A sequences or SDMs were evaluated for NS5A inhibitor susceptibility

Results: NS5A inhibitor RAVs were detected in 11/71 (15.5%) GT1a viruses: M28T=3, Q30H=4, L31M=3 and Y93C/H/N=6. Among the 11 viruses with GT1a RAVs, six harbored a single RAV while five had more than one RAV. RAVs were present at >10% (range: 13.6-99.2%) of the quasispecies in 6/11 viruses and at <10% (range: 0.92-3.1%) for the remaining five viruses. Similarly, major NS5A RAVs were detected in 7/38 (18.4%) GT1b viruses: L31M=1, Y93H=7. RAVs were present at >10% (range: 20.7-98.8%) of the quasispecies in 2/7 viruses and at <10% (range: 0.54-1.1%) for the remaining five viruses. Codons for all observed RAVs differed by only one nucleotide from the predominant "wild type" codon, except L31M in GT1b. Replicons containing patient NS5A sequences with RAVs exhibited large reductions in susceptibility to NS5A inhibitors. Reductions in NS5A inhibitor susceptibility were greater when RAVs were tested in the context of GT1a NS5A sequences (FC >150) compared to GT1b NS5A sequences (FC<20).

Conclusions: The prevalence of resistant variants was similar between GT1a and GT1b isolates. Naturally occurring NS5A resistance variants were more diverse among GT1a viruses, compared to GT1b. Slightly higher proportions of resistant variants were present within GT1a virus populations compared to GT1b. The combination of multiple resistance pathways, lower genetic and resistance barriers may provide advantages for GT1a viruses to escape NS5A inhibition.

697 Hepatitis C Q80K Prevalence in BC, Canada, Determined by a Public Domain Assay

Jeffrey B. Joy[1]; Celia K. Chui[1]; Chanson J. Brumme[1]; Mel Krajden[2]; Andrea Olmstead[2]; Winnie Dong[1]; Wendy Zhang[1]; Aram Karakas[1]; Huong Hew[3]; Richard Harrigan[1]

[1]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; [2]BC Centre for Disease Control, Vancouver, Canada; [3]Janssen Pharmaceuticals, Inc., Toronto, Canada

Background: HCV genotype 1a (GT1a) infections harbouring a baseline Q80K polymorphism in the NS3 gene have reduced virologic response to IFN-based HCV treatments containing simeprevir. We aimed to develop, validate, and freely disseminate a NS3 clinical sequencing assay to detect Q80K and other NS3 mutations, and establish their prevalence in British Columbia (BC), Canada.

Methods: RNA was extracted using a NucliSens easyMag, amplified by nested RT-PCR and sequenced by Sanger or Illumina sequencing. Sanger chromatogram interpretations were performed automatically using in-house analysis software (ReCall). HCV genotypes were identified using INNO-LiPA HCV 2.0 (5'UTR); sequence-based genotype assignment was verified phylogenetically in comparison with reference sequences. Our assay was validated via comparison with 70 sequences from an external laboratory and relative to consensus sequences from next-generation sequencing (MiSeq). To establish the prevalence of Q80K in BC, samples from 376 GT1 LiPA HCV+ individuals diagnosed in 2011 were examined. Sequences were also screened for mutations associated with boceprevir/telaprevir resistance.

Results: Comparison of sequences generated by an external lab and with MiSeq consensus sequences revealed > 98% sequence concordance, and no discordant calls of Q80K. LiPA identified 231 (61%) individuals as GT1a, 91 (24%) as GT1b, while subtype could not be resolved in 54 cases (14%). The prevalence of Q80K was 61%, 11%, and 50% in LiPA GT1a, 1b and unresolved, respectively. Sequence analysis suggested that 52/54 individuals (96%) whose LiPA genotype was unresolved were actually GT1a, as were 28/91 (44%) cases that LiPA identified as 1b. Using a sequence-based assessment of HCV genotype, the prevalence of Q80K was 176/309 (57%) in GT1a compared to 1/66 (2%) in GT1b. Mutations associated with boceprevir or telaprevir resistance in this newly diagnosed population were also observed (V36M, N=2; T54S, N=5; and R155K, N=3).

Conclusions: Our results suggest the overall prevalence of Q80K in GT1 in BC is 47%. Q80K was highly prevalent where LiPA results could not resolve GT1a vs 1b. Inconsistent HCV genotype 1a vs 1b assignment by LiPA UTR in comparison to sequence-based genotyping suggests that all individuals with GT1 HCV infection in BC should be screened for the Q80K polymorphism. Assay details and software are freely available to academic labs.

698 HCVNS3 Variants in HIV/HCV Coinfected Patients Before-After PegIFN/Ribavirin

Enass Abdel-Hameed[1]; Susan D. Rouster[1]; Xiang Zhang[2]; Jing Chen[2]; Mario Medvedovic[2]; Kenneth E. Sherman[1]

[1]University of Cincinnati, Cincinnati, OH, US; [2]University of Cincinnati, Cincinnati, OH, US

Background: This study was designed to characterize HCV NS3 protease resistance associated variants (RAVs) by deep sequence analysis at baseline and after 12 weeks of PegIFN / ribavirin treatment in subjects who failed to achieve an early viral response. Overall genetic variability at NS3 protease drug resistant sites was also assessed.

Methods: Thirty HCV/ HIV coinfected subjects were evaluated. All subjects were previously enrolled/consented in ACTG 5178 (SLAM-C), a study designed to evaluate the effects of prolonged PegIFN on hepatic fibrosis. An RT-PCR-amplified NS3 product was fragmented and primed into a sequencing library. The individually pooled libraries were sequenced with Illumina HiSeq next generation sequencing system set for single read.

Results: The study cohort was predominantly male (83.3%), with a median age of 45years. 40% were white and 56.7% black. Baseline mean HCV $\log_{10}$ viral load was 6.6 and HIV viral load was 3365.1. 56.7% had undetectable HIV due to effective cART. IL28B distribution for C/C, C/T, and T/T were 35, 45, and 20 % respectively. Sixteen patients were genotype 1a, 2 were 1a1b and 12 were type 1 no subtype. At baseline, protease RAVs was present in 73.3% of patients and expanded to 83.3 % of patients after 12 weeks. At baseline RAVs, V36L, T54S, T54A, and V55A were each detected in 3% of patients. V36M was detected in 4% of patients.I170V was present in 37% of patients. Q80K showed the highest prevalence at 44%. After 12 weeks of treatment, V55I and V36M expanded to 9% and 12 % of the population respectively, while Q80K was now detected in 50 % of the patients with a positive correlation to liver fibrosis stage (r= 0.5235, p=0.031). The proportion of subjects having detectable I170V decreased to 20% of patients. Over all amino acid positions studied, no statistical difference in relative abundance of RAVs within a patient before-after 12 weeks of treatment was seen. There was no relationship to IL28B, viral loads, age, gender or race.

Conclusions: Key RAVs for HCV protease inhibitors are present in the majority of the HCV/HIV coinfected population prior to therapy. Correlation of Q80K with fibrosis stage suggests that compartmentalization within the liver may contribute to persistence of mutations less fit than wildtype. The prevalence of V36M and Q80K appears to be increased following therapy with PegIFN /ribavirin suggesting that pressure from non-targeted therapies could lead to selection.

699 Compensatory Mutations in HCV NS5A/B Coevolve in Patients Failing NS3 Inhibitors

Velia Chiara Di Maio[1]; Valeria Cento[1]; Daniele Di Paolo[2]; Sergio Babudieri[3]; Gloria Taliani[4]; Giustino Parruti[5]; Giuliano Rizzardini[6]; Mario Angelico[2]; Carlo Federico Perno[1]; **Francesca Ceccherini-Silberstein**[1]

[1]University of Rome Tor Vergata, Rome, Italy; [2]University Hospital of Rome Tor Vergata, Rome, Italy; [3]University of Sassari, Sassari, Italy; [4]University of Rome La Sapienza, Rome, Italy; [5]Pescara General Hospital, Pescara, Italy; [6]Hospital Sacco of Milan, Milan, Italy

Background: The monocistronic structure of HCV genome may imply a coevolution of all genes during protease inhibitors (PI) failure. Our aim was to analyze baseline to failure evolution of NS3/NS5A/NS5B in PI-failing patients.

Methods: Twenty patients (15 GT1a; 5 GT1b) experiencing virological-failure with peg-IFN/riba+boceprevir (5), +telaprevir (13) or +simeprevir (2) were analyzed. NS3-protease, NS5A and NS5B sequences were obtained in all patients at baseline and at PI-failure, by population sequencing.

Results: Subtyping information was confirmed by phylogenetic analysis of NS3, NS5A and NS5B sequences. Baseline $_{NS3}$RAVs were detected in 6/20 patients, all GT1a infected (1=V36L+Q80K, 4=Q80K, 1=R155K). In addition, 3/20 patients presented $_{NS5A}$RAVs (1GT1a and 1GT1b=L31M, 1GT1b=Q54H) and 4/20 $_{NS5B}$RAVs to non-nucleosidic inhibitors (3GT1a=A421V, 1GT1b= A421V). Only one GT1a patient showed natural resistance simultaneously in NS3 (Q80K) and NS5A (L31M).

At failure, all 15 GT1a and 4/5 GT1b patients presented major $_{NS3}$RAVs. Prevalence of resistance mutations changed according to subtype (1a: 1=V36L+R155M; 8=V36M+R155K/T; 1=T54S+R155K; 1=T54A+R155T; 1=V55A+R155T; 3=R155K; 1b: 1=T54A+V170A; 1=F43C+T54S+A156T; 1=T54S+A156T+V170A; 1=A156T).

$_{NS5A/NS5B}$RAVs detected at baseline were still present and no other RAVs developed outside the NS3 region. However, 18/20 patients developed *de novo* $_{NS5A}$mutations (median[IQR] number=2[1-3]) and/or $_{NS5B}$mutations (median[IQR]number=1[1-2]). 2 patients didn't show any evidence of *de novo* $_{NS5A/NS5B}$mutations. Putative IFN-resistance associated NS5A-mutations remained unaffected by treatment-failure. Comparing baseline/failure sequences, statistically significant differences in entropy were observed only in NS3 RAV positions.

Among GT1a patients, covariation analysis across all 3 genes showed several patterns of significantly associated mutations: $_{NS3}$Q80K was significantly associated with $_{NS5A}$D441G (p=0.002,phy=0.87), as well as with $_{NS5A}$R311Q and $_{NS5B}$S506T (p=0.02,phy=0.70, for both cases). Instead, a negative association was observed for $_{NS3}$R155K and $_{NS5B}$S506T (p=0.03,phy=-0.78). Interestingly, 2/3 GT1a patients with $_{NS5B}$S506T failed without developing the classical $_{NS3}$R155K, but with the development of $_{NS3}$R155M and $_{NS3}$R155T+V55A, respectively.

Conclusions: This proof-of-concept study shows that mutations in NS5A and NS5B may coevolve with NS3 RAVs during PI-treatment, potentially acting as compensatory mutations for viral fitness.

THURSDAY, FEBRUARY 26, 2015

Session P-N11 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Other Hepatitis Viruses: HBV, HDV, HEV

700 Hepatitis B Vaccine Response in Children Attending Rwanda Military Hospital

Judy T. Orikiiriza[1]; Louis Mujuwisha[2]; Elizabeth Karlsson[3]; Vincent Mutabazi[4]; Johan Normark[3]

[1]Infectious Diseases Institute Makerere College of Health Sciences, Kampala, Uganda; [2]University of Rwanda, Kigali, Rwanda; [3]Umea Infectious Diseases Institute, Kigali, Sweden; [4]Rwanda Biomedical Center, Kigali, Rwanda

Background: Hepatitis B virus (HBV) vaccine is protective in over 85% thus in most low resource settings (LRS) governments have endeavored to prioritize HB vaccination. There is paucity of information in LRSs concerning impact of HBV vaccination in pediatrics. Our general objective was to assess the humoral response to Hepatitis B vaccine in pediatric patients attending Rwanda Military Hospital.

Methods: This was a prospective cross sectional study at Rwanda Military Hospital from October 2013 –December 2013. Children aged 3.5 months -18 years were enrolled consecutively after fulfilling the study criteria. A standardized questionnaire was used to capture demographic parameters of participants. Blood samples were removed to carry out HBsAg, antibodies to the HBsAg and HIV. Data was entered and analyzed using STATA version 1 2. Ethical approval was sought from the Institutional Review Board at RMH and College of Medicine and Health Sciences School of Medicine University of Rwanda.

Results: Three hundred and four children were analysed, with a male: female ratio of 1.4:1, age range of 3.5 months to 18 years with a mean age of 7.88 years (SD= ±5.5 years). Prevalence of HBV infection was 12/248(4.8%) and mean age of HBV infected children was 12.7 years (age range: 2.75-18 years). It was highest 9/12(75%) in >11-18 years age group with a male: female ratio of 10:2. HIV prevalence was found to be 1.6% with no HBV-HIV co-infection.

Reported vaccination rate by the primary care taker was found to be 214/304(70.4%), 108/247(35.5%) were found to have Abs HBsAg titer >10IU that conferred protection. Protective vaccination titers were found to be 61.9% and 10.3% for ages between 3.5 months-11 year, >11year-18 years respectively. Of those reported to be vaccinated 59.9% had adequate Abs HBsAg titers and the proportion of Abs HBsAg levels decreased with increasing age with a p value<0.001.

Conclusions: Abs to HBsAg wane with age amongst the vaccinated group and the commonest age group with high HB infection was in the older age thus there is need for providing HB vaccination boosters for the older age group to maximise HB prevention strategies. There is need to provide HB treatment beyond the HIV positive people as our study clearly demonstrates that those infected by HBV were all HIV negative.

A larger study is recommended to determine the predictors of low HB antibody titers in our children and to come up with the appropriate timing for booster doses so that more relevant vaccine programs are rolled out.

701 Revaccinating HIV+ Adults With Double vs Standard HBV Regimen: ANRS B-BOOST Trial

David Rey[1]; Cécilie Dufour[2]; Marie-Josée Wendling[3]; Patrick Miailhes[4]; Philippe Sogni[8]; Georges Haour[2]; Marie-Louise Michel[7]; Lionel Piroth[6]; Odile Launay[5]; Fabrice Carrat[2]

[1]University Hospital Strasbourg, Strasbourg, France; [2]Université Pierre et Marie Curie, Strasbourg, France; [3]Hôpitaux Universitaires Strasbourg, Strasbourg, France; [4]University Hospital of Lyon, Lyon, France; [5]CIC Vaccinologie, Paris, France; [6]University Hospital of Dijon, Dijon, France; [7]Institut Pasteur, Paris, France; [8]Cochin Hospital, Paris, France

Background: Immune response to standard hepatitis B (HBV) vaccination is decreased in HIV-infected patients, and it has been recently shown that a double dose HBV primary vaccination regimen improved serological response. However, the immunogenicity of this regimen in non responders to a previous vaccination is unknown.

Methods: In an open-label, multicenter, 1:1 parallel groups randomized clinical trial, stratified according to CD4 cell count (200-349, and > 350 cells/μl), 411 HIV-infected adults, CD4 T cells ≥ 200/μl, and previously vaccinated against HBV, without HBV markers, received a booster dose (20 μg) of HBV vaccine. 178 of them who did not respond to the boost were randomized to receive HBV vaccination with either 3 intramuscular (IM) standard doses (20 μg, group A, n=90), or 3 IM double doses (40 μg, group B, n=88) at weeks 0, 4 and 24. Subjects with anti-HBs ≥ 10 mUI/mL and ≥ 100 mUI/mL at week 28 were defined as responders (main endpoint) and high responders, respectively.

Results: The median age of the population was 44 years (IQR 40-51); 78% were male; the median CD4 cell count was 512 cells/μl (IQR 424-682); 71% had plasma viral load < 50 copies/ml. In an intent-to-treat analysis (missing = failures), the percentage of responders and high responders were 67% and 26% in group A, 74% and 47% in group B (P=.33 and P=.002). At week 28, the geometric mean titre of anti-HBs were 20 and 60 mUI/mL in group A and B respectively (P=.0004). BMI was the only factor associated with response to vaccination (>=25 vs <25, odds-ratio=2.42; 95%CI (1.1-5.3) P=.028). Among responders at week 28, 43% and 64% in group A and B respectively, had anti-HBs ≥ 10 mUI/mL at week 72 (p=.0069), and geometric mean titre of anti-HBs were 11 and 35 mUI/mL (p=.0016) in group A and B at week 72. There were two serious adverse events associated with the vaccine (1 in each group): exacerbation of psoriasis and severe headaches. Local reactions occurred in 5% of patients in group A versus 15% in group B (P=.02).

Conclusions: In HIV-1 infected adults who did not respond to a standard dose HBV vaccination, a double-dose re-vaccination regimen does not increase the response rate but provides higher level of anti-HBs titre, with longer durability, compared with a standard re-vaccination regimen.

702 Complex HBV Quasispecies Affects Immunogenicity in Acute Hepatitis B Infection

Valentina Svicher[1]; Marianna Aragri[1]; Nicola Coppola[2]; Claudia Alteri[1]; Arianna Battisti[1]; Caterina Sagnelli[2]; Mariantonietta Pisaturo[2]; MariaConcetta Bellocchi[1]; Evangelista Sagnelli[2]; Carlo-Federico Perno[1]

[1]University of Rome Tor Vergata, Rome, Italy; [2]Second University of Naples, Naples, Italy

Background: To identify HBV RT and HBsAg quasispecies heterogeneity in patients with acute hepatitis B (AHB) and to define their clinical value.

Methods: This study included 62 HBsAg+ and IgM/anti-HBc+ patients with clinical and biochemical signs of AHB (44 infected by genotype [gen] D and 18 by gen A) observed from 2000 to 2010. Ultra-deep sequencing (UDPS) was performed on plasma samples obtained at first observation. Drug-resistance and immune-escape mutations were retrieved from literature. Shannon Entropy (weighted for the intra-patient prevalence of each mutated position) was used to measure the extent of amino acid variability of HBsAg positions.

Results: 75.8% of patients were male with median (IQR) age of 36(29-46)years. Median (IQR) ALT and median (IQR) serum HBV-DNA were 2,544(1,938-3,078)U/L and 5.88(4.47-7.37)$\log_{10}$IU/ml. 61/62 became HBsAg-negative with 33/61 developing anti-HBs (marker of full immune control).

By UDPS, drug resistance mutations (rtV173L/rtL180M/rtA181T/rtA194T/rtM204I) were detected in 8.1% of patients with an intra-patient prevalence ranging from 0.11% for rtA181T to 99.98% for rtL180M.

UDPS also detected ≥1 immune-escape mutation within the a-determinant in 48.4% of patients with an intra-patient prevalence from 0.16% to 100%. Among them, vaccine-escape mutations were found only in gen D. This is the case of sG145R, sM133L, and sP120S, detected in 11.4% of patients, with an intra-patient prevalence ranging from 3.9% to 99.9% for sG145R, from 1.9% to 16.8% for sM133L, and from 100% to 100% for sP120S.

Similarly, stop-codons were found in 19.3% patients (intra-patient prevalence range:1.6%-47.5%). They occurred at 11 HBsAg positions including 172 and 182 known to correlate with an increased HBV oncogenic potential.

Finally, in gen D, an higher Shannon Entropy at specific HBsAg positions correlated with no anti-HBs production. Among them, positions 130 and 133 (localized in HLA class II epitope ranging aa 124-137) were found mutated only in patients not developing anti-HBs (1.98±0.011 vs 0, and 1.95±0.033 vs 0, respectively, P<0.05).

Conclusions: A substantial fraction of AHB-patients is characterized by a complex viral quasispecies with reduced antigenicity/immunogenicity, enhanced oncogenic-potential and/or altered drug-susceptibility. These viral variants may potentially expose patients to severe and/or difficult-to-treat forms of HBV-infection (also in the setting of HBV reactivation), and may affect the efficacy of current HBV vaccination strategy.

703 Higher Rate of Hepatitis B Antigen and Anti-HBV Antibody Seroconversion Among HIV/Chronic Hepatitis B Coinfection Initiating HBV Active HAART From Thailand

Anchalee Avihingsanon[1]; Opass Putcharoen[2]; Salyavit Chittmittrapap[2]; Tanakorn Apornpong[1]; Vorapot Sapsirisavat[1]; Sasiwimol Ubolyam[1]; Stephen J. Kerr[1]; Kiat Ruxrungtham[1]
On behalf of the HIV-NAT 105 Study Team

[1]HIV Netherlands Australia Thailand Research Collaboration, Thai Red Cross - AIDS Research Centre, Patumwan, Thailand; [2]Chulalongkorn University, Bangkok, Thailand

Background: Hepatitis B surface antigen (HBsAg) loss is considered the ideal outcome of chronic hepatitis B virus (HBV) infection. HBsAg loss was reported in 12% of subjects from a Caucasian HIV/HBV cohort. We investigated the rate and predictors of HBsAg loss and antiHBs Ab seroconversion among 213 HIV/HBV coinfected patients from Thailand.

Methods: Subjects with confirmed chronic HBV infection (HBsAg positive results >6 months apart) were selected from the cohort. Serial HBV serology, HBV DNA, quantitative HBsAg and liver biochemistry were performed.

Results: Of 213 subjects enrolled, median age was 42 (IQR 36 – 48) years, 69% were male. At start of ART, CD4 cell count was 242 (IQR 107-371) cells/ mm^3 At the most recent visit, median CD4 cell count was 523 cells/mm^3, 84% had undetectable HIV RNA, 56% were HBeAg positive and 82.4% had HBV genotype C. Median baseline HBV DNA was 7.2 (IQR 3.2-7.5) $\log_{10}$ IU/mL. Loss rate of HBeAg (for HBeAg positive cases) and HBsAg were 44% and 17.4%, respectively. The incidence of HBsAg conversion was 2.93(2.13-4.05) per 100 PY. 15/37 patients (40.5%) developed antiHBsAb conversion at a median duration of 163 weeks after ART. Baseline demographic data was comparable between those with and without HBsAg loss. Median duration on ART was 9 (IQR 3-14) years, with 68.5% on ART for >5 years. However, duration of ART was longer for those with HBsAg loss (12 vs 8 yrs). Overall, 80.2% had HBV DNA <10 IU/mL at the most recent clinic visit. 27 and 8 patients were on low dose and discontinued of tenofovir, respectively, due to falling eGFR. All of these had HBV DNA < 10 IU/mL at last visit. HBsAg loss was associated with younger age [harzard ratio:HR 0.94 (95% confidence interval:95% CI 0.89-0.99), p=0.019] and normal ALT [HR 3.16 (95% CI 1.11-9.02)]. In a subgroup with available HBsAg that had been quantitated, levels >100 IU/mL [HR 0.02 (95%CI 0.03-0.21), p<0.001] was associated with a lower clearance of HBsAg than those with levels ≤100 IU/mL in adjusted analyses.

Conclusions: Rate of HBsAg loss, HBeAg and antiHBsAb seroconverstion in these Asian HIV/HBV coinfected individuals initiating HBV active ART were high. Older age and abnormal ALT were associated with reduced HBsAg clearance. This population is a promising target for studies exploring intensive biomarkers for potential HBV cure.

704 Occult HBV/HIV Coinfection and Validation of Cost-Effective NAT Pooling PCR

Shanmugam Saravanan[1]; Janardhanan Mohanakrishnan[1]; Thongadi Ramesh Dinesha[1]; Jayaseelan Boobalan[1]; Pachamuthu Balakrishnan[1]; Kailapuri G Murugavel[1]; Sunil S Solomon[2]; Suniti Solomon[1]; Davey M. Smith[3]

[1]YRG Centre for AIDS Research and Education, Chennai, India; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]University of California San Diego, San Diego, CA, US

Background: Owing to the cost of HBV viral loads, in most resource-limited settings (RLS) only HBsAg testing is done. This leads to under diagnosis of HBV infection by ignoring occult HBV infection (OHI). Thus, we studied the prevalence of HBV and OHI among HIV infected individuals and evaluated a pooling HBV nucleic acid test (NAT) as a cost-effective alternative to conventional HBV viral load test

Methods: ART-naïve, 502 HIV-1 infected individuals visiting YRG CARE were enrolled; median age was 36 years (IQR 31-40) and CD4 count was 381.5 cells/μL (IQR 232.5-540.25). HBV infection was detected by HBsAg ELISA (Genedia, Korea) followed by anti-HBc, anti-HBs ELISA (DiaSorin, Italy) and HBV DNA PCR was performed among all HBsAg negative individuals to find OHI. Pooling HBV NAT was performed in a matrix of 5x5 pooled samples, i.e. 25 plasma samples, and was evaluated against the gold standard HBV viral load (Abbott HBV RealTime PCR, linearity 1 - 9 log IU/mL) for cost and accuracy

Results: The prevalence of HIV/HBV co-infection by HBsAg positivity was 6% (32/502, 95% CI 4.5%-8.86%). To test for OHI, we randomly selected 270 HBsAg negative individuals and performed HBV viral loads, anti-HBc and anti-HBs ELISA and found an overall prevalence of OHI as 10% (27/270, 95% CI 6.81%-1.44%) based on HBV DNA positivity, of which 96.3% (26/27) and 25.9% (7/27) were positive for anti-HBc and anti-HBs, respectively. This shows OHI is associated with anti-HBc alone (OR 9.46, *p* 0.1846) compared to anti-HBs. Compared to individual HBV viral loads, pooling HBV NAT had a positive predictive value of 100% and negative predictive value of 96.43%, with 100% specificity and 66.67% sensitivity. There would also have been cost (37$ vs. 91$) saving with pooling HBV NAT

Conclusions: The prevalence of OHI is high among HIV-infected individuals in India, which would be missed by routine serology tests, thus HBV DNA testing should also be considered. However, conventional HBV viral loads are expensive in RLS, thus pooling HBV NAT should be considered, as it could reduce assay costs by up to 40%

705 Invariant Natural Killer T-Cells in HIV-HBV Coinfection

Matteo Basilissi[1]; Camilla Tincati[1]; Esther Merlini[1]; Elisabetta Sinigaglia[2]; Javier Sanchez-Martinez[2]; Giovanni Carpani[2]; Antonella d'Arminio Monforte[1]; Laura Milazzo[1]; Giulia Marchetti[1]

[1]University of Milan, Milan, Italy; [2]San Paolo Hospital, Milan, Italy

Background: HIV+HBV+ co-infected patients (pts) are at risk of hepatic disease progression, despite effective treatment. The dysregulation of the immune response in HIV may affect the course of HBV disease. Given that invariant Natural Killer T (iNKT) cells mediate viral liver disease and HIV infection, we hypothesized a role for this cell subset in HIV+HBV+ co-infection.

Methods: Cross-sectional study: a) HIV+HBV+ (10 pts treated with TDF/FTC; 4 naïve pts); b) HIV+ (10 treated pts, 5 naive pts); c) HBV+ (9 treated pts; 5 naïve pts); d) HIV-HBV- (5 pts). iNKT frequency (CD3+Vα24+CD1d+), CD161 expression and TNF-α/IFN-γ release prior to and after PMA/Ionomycin and αGalactosylCeramide (αGalCer) were measured by flow cytometry. Kruskal-Wallis and Wilcoxon tests were used for statistics.

Results: In HIV+HBV+, a negative correlation was found between AST levels and cytokine release upon αGalCer (TNF-α: p=0.014, r=-0.65; IFN-γ: p=0.06, r=-0.53). No other significant correlations were found between iNKT phenotype/function and liver function enzymes in the other groups. To better understand the uniqueness of iNKT cells in HIV+HBV+ co-infection versus HIV and HBV infections alone, we conducted a comparative analysis of iNKT cell frequency, phenotype and function among study groups according to their treatment status (i.e. therapy-naïve and treatment-experienced subjects).

Therapy-naïve (mono-infected HBV or HIV and co-infected) showed similar circulating iNKT cells (p=0.46), CD161 expression (p=0.3), IFN-γ (unstimulated, p=0.6; PMA/Iono p=0.8; αGalCer p=0.07) and TNF-α production (us, p=0.09; PMA/Iono p=0.4; αGalCer, p= 0.9) to HIV-HBV- uninfected controls.

Treated subjects showed comparable iNKT frequencies (p=0.8) and CD161 expression (p=0.9) among study groups. Interestingly, HIV-infected individuals showed a peculiar functional capacity of iNKT cells. Indeed, mono-infected HIV+ showed the highest constitutive release of TNF-α (77%, IQR; 69-86; p=0.008) and PMA/Iono-stimulated IFN-γ production (85%, IQR: 77-94; p=0.009). Further, only iNKT cells from co-infected HIV+HBV+ significantly increased TNF-α release after αGalCer (p=0.04). No statistical differences were registered in terms of iNKT function in HBV mono-infection.

Conclusions: The inverse correlation between iNKT and liver function in HIV+HBV+ suggests the impairment of circulating iNKT cells in response to increased liver inflammation. HIV, yet not HBV, appears to be the main driver of iNKT activation in HIV+HBV+ co-infected subjects on treatment.

706 Effect of Immunosuppression and Antivirals on Intracellular HBV Replication in HIV-HBV Coinfection

Anders C. Boyd[1]; Karine Lacombe[1]; Fabien Lavocat[2]; Sarah Maylin[3]; Patrick Miailhes[4]; Caroline Lascoux-Combe[5]; Constance Delaugerre[3]; Pierre-Marie Girard[1]; Fabien Zoulim[2]

[1]Inserm UMR_S1136, Paris, France; [2]Inserm U1052, Lyon, France; [3]Inserm U941, Paris, France; [4]Hospices Civils de Lyon, Lyon, France; [5]Hôpital Saint-Louis AP-HP, Paris, France

Background: Covalently closed circular DNA (ccc-DNA) of hepatitis B virus (HBV) acts as a reservoir for reactivation of viral replication and whose quantification can be used as a marker of persistent intracellular replication. The determinants of intracellular levels of replication have rarely been evaluated in HBV-human immunodeficiency virus (HIV) co-infected patients.

Methods: Sixty HIV-HBV co-infected patients with at least one liver biopsy during follow-up in the French HIV-HBV cohort were included. HBV ccc-DNA and total intracellular HBV-DNA were extracted from biopsies and quantified by real-time PCR. Risk-factors of intracellular replication were determined using mixed-effect linear regression models.

Results: At the time of biopsy, 35 (61.4%) patients were HBeAg-positive and 23 (46.9%) had detectable serum HBV-DNA (median: 3.10 log10 IU/mL, IQR:2.75-5.38). Among the 22 patients undergoing tenofovir (TDF)-containing antiretroviral therapy, cumulative TDF-duration was at a median 17.8 months (IQR:5.7-31.0). Overall, median HBV ccc-DNA was -1.10 log10 copies/cell (IQR:-1.70, -0.29) and total intracellular HBV-DNA was 0.27 log10 copies/cell (IQR:-0.39, 2.00). In multivariable analysis, patients with HBeAg-positive serology had significantly higher levels of HBV ccc-DNA (+0.76 log10 copies/mL; 95%CI:0.39, 1.13; $p<0.001$), whereas those with a nadir CD4+ cell count above 250/mm3 had significantly lower HBV ccc-DNA levels (-0.57 log10 copies/mL; 95%CI:-0.95, -0.19; $p=0.004$). Furthermore, patients with longer than 3 years of cumulative TDF-duration had significantly lower HBV ccc-DNA levels after adjustment (-0.88 log10 copies/cell: 95%CI:-1.40, -0.35; $p=0.001$). Accordingly, when focusing on patients undergoing TDF with a biopsy at TDF-initiation and sometime during therapy (median duration: 35.3 months, range: 20.2-56.6), most exhibited strong declines in HBV ccc-DNA (median change in log10 copies/cell/year:-0.46, range:-0.67, 0; $n=7$). HBV ccc-DNA levels did remain detectable at the end of follow-up for all patients, yet at very low levels (median: 0.04 copies/cell, range:0.01, 0.31). The results above were similar when using total intracellular HBV-DNA levels as an end-point.

Conclusions: In coinfected patients, severe immunosuppression is associated with intracellular HBV replication. Treatment with TDF is linked to large declines in ccc-DNA, yet replication within the hepatocyte still persists after long periods of treatment.

707 Prevalence of HDV in a Midwestern HIV-HBV Coinfected Population

Sanam Razeghi; Susan Rouster; Kenneth E. Sherman
University of Cincinnati, Cincinnati, OH, US

Background: Hepatitis D virus (HDV), a defective RNA virus leads to the most aggressive form of viral hepatitis. HDV is thought to be relatively uncommon in the U.S. and its prevalence and significance in those with HIV is virtually unknown. Furthermore, serologic detection methods may under-represent true prevalence. We sought to assess the prevalence of HDV RNA in a Midwestern cohort of patients with HBV-HIV coinfection and a comparison group with HBV alone.

Methods: We developed and validated a qRT-PCR methodology for detection of HDV RNA. Briefly, viral RNA was extracted using a QIAamp viral RNA mini kit, followed by qRT-PCR in a BioRad CFX96 platform. A 93 BP region was amplified. The assay was validated by sequence analysis of the amplicon products with comparison to published sequences. The initial cohort was then tested and associated clinical data were obtained. Statistical analysis was performed using Statistix 10.0.

Results: 138 subjects (48 HBV-positive/HIV-negative and 90 HBV-positive/HIV-positive) were evaluated. The mean age was 38. 83% were male. 17% were on HBV active therapy. Two subjects were found to be HDV RNA positive, both from the HBV/HIV group. The mean ALT level in the HDV positives was 228 U/L vs. 96 U/L in HDV negative. Both were African-American; one was born in the U.S. and the other in Africa. Cirrhosis was not present in either patient. Neither reported IDU as a risk factor. No samples were positive in the cohort with HBV alone.

Conclusions: Our analysis suggests HDV prevalence in those with HBV/HIV coinfection of 2% ($p = 0.2$, CI 0-5.3%) as compared to 0% in the HIV-negative cohort. Cirrhosis was not present in either subject found to have HDV coinfection though mean ALT level was higher. Further analysis of larger cohorts appears warranted because presence of HDV RNA was unsuspected in these patients.

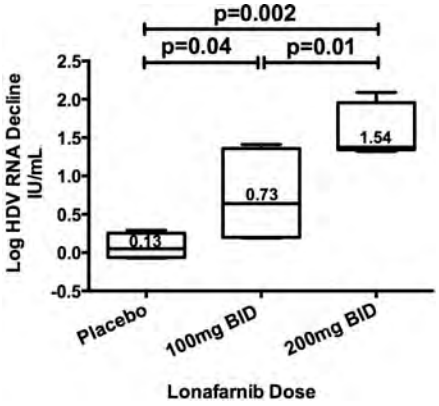
708LB Oral Prenylation Inhibition With Lonafarnib in Chronic Hepatitis D Infection: A Randomized, Double-Blinded, Placebo-Controlled Proof-of-Concept Study

Christopher Koh[1]; Laetitia Canini[7]; Harel Dahari[2]; David Cory[3]; Ingrid Choong[3]; David Kleiner[4]; Stewart Cooper[6]; Mark A. Winters[5]; Jeffrey Glenn[5]; Theo Heller[1]
[1]National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Fulton, MD, US; [2]Loyola University Medical Center, Maywood, IL, US; [3]Eiger BioPharmaceuticals, San Carlos, CA, US; [4]National Cancer Institute, Bethesda, MD, US; [5]Stanford University, Stanford, CA, US; [6]California Pacific Medical Center, Palo Alto, CA, US; [7]University of Edinburgh, Edinburgh, United Kingdom

Background: Interferon therapy for chronic delta hepatitis (HDV) infection is unsatisfactory. In *in vivo* models, prenylation inhibition has proven effectiveness against HDV. In a first-in-human for HDV, proof-of-concept study, we evaluated the antiviral effects and safety of the prenylation inhibitor, lonafarnib (LNF), in patients with chronic HDV.

Methods: HDV patients were sequentially enrolled into 2 groups in a phase 2a double-blinded, randomized, placebo-controlled study and received: LNF 100 mg (Group 1) or LNF 200 mg (Group 2) twice daily for 28 days followed by 6 months of follow-up. Both groups enrolled 6 treatment and 2 placebo subjects, where Group 1 placebo subjects were offered open-label LNF in Group 2. Patients had 72-hour viral kinetic and pharmacokinetic evaluations at the start of therapy. Serial measurements of safety parameters, liver tests, pharmacokinetics, and virologic (HDV RNA and HBV DNA) markers were obtained. Mathematical modeling of HDV clearance and LNF effectiveness was performed.

Results: In this completed study, the 14 patients were mostly male (71%) with a median age of 38 years and included Asian (50%), Caucasian (43%) and African (7%) subjects. Median baseline evaluations include: ALT (89 IU/mL), AST (61 IU/mL), Ishak fibrosis (3), HBV DNA (<21 IU/mL) and HDV RNA ($1.01x10^6$ IU/mL). There were no differences in baseline parameters between groups. After 28 days of therapy, compared to placebo, the mean log HDV RNA decline from baseline was 0.73 log IU/mL in Group 1 ($p=0.04$) and 1.54 log IU/mL in Group 2 ($p=0.002$). LNF serum concentrations correlated with HDV RNA change ($r^2=0.78$, $p<0.0001$). HDV RNA decay was biphasic in most patients. The 1st phase lasted 9.0 (IQR=7.6;14.0) vs. 5.0 (IQR=4.1;6.0) days (Group 2 vs. Group 1) with greater decline in Group 2 vs. Group 1 (1.35 [IQR=1.34;1.51] vs. 0.61 [IQR=0.42;0.83] log IU/ml). The overall 2nd phase decline slope was -0.12 (IQR=-0.18;-0.01) log IU/wk. There were no treatment discontinuations due to adverse events and no evidence of virologic resistance. Adverse events included mild to moderate nausea, vomiting, dyspepsia, anorexia, diarrhea, and weight loss.



HDV RNA Decline After 28 Days of Lonafarnib Therapy

Conclusions: This is the first demonstration in patients that treatment of chronic HDV with the prenylation inhibitor LNF significantly reduces virus levels. The decline in virus levels significantly correlated with serum drug levels, providing further evidence for the efficacy of prenylation inhibition in chronic HDV.

709 Incidence of Hepatitis E Virus in HIV-Infected Patients: A Longitudinal Prospective Study

Antonio Rivero-Juarez[1]; Loreto Martinez-Dueñas[1]; Antonio Martinez-Peinado[2]; Angela Camacho[1]; Celia Cifuentes[3]; Ana Gordon[1]; Mario Frias[1]; Julian Torre-Cisneros[1]; Juan A. Pineda[3]; Antonio Rivero[1]
[1]Instituto Maimonides de Investigación Biomédica de Córdoba, Cordoba, Spain; [2]Instituto Maimonides de Investigación Biomedica de Córdoba, Cordoba, Spain; [3]Hospital Universitario de Valme, Seville, Spain

Background: Hepatitis E virus (HEV) incidence in HIV infected patients has not been well established. Studies reporting HEV seroprevalence and incidence in this populations present several methodological limitations such as retrospective analysis and small population samples. As a result, the current magnitude of this emerging disease in this population cannot be established. Therefore, we designed a study to evaluate the incidence of HEV and its clinical implications in HIV infected patients.

Methods: Prospective study in Southern Spain that included HIV-infected patients who were followed up between September 2012 and July 2014. All patients included were tested for anti-HEV IgG using EIA (Wantai HEV-IgG ELISA). All anti-HEV negative patients were prospectively followed-up during 1 year. In these patients an EIA anti-HEV IgG was performed each 6. In those patients with anti-HEV IgG positive, a RT-PCR was performed (amplicube HEV). Clinical and demographic variables were collected at baseline and during the follow-up. Incidence rate was calculated.

Results: Eight-hundred and ninety two patients were included at baseline. Of them, 188 (21.07%) showed positive for anti-HEV IgG, consequently, 704 patients were included in the study. Six-hundred and twenty-one (88.2%) complete the study period. The median follow-up (interquartile range) was 11.96 months (8.52-14.52). Thirty-four (5.4%) patients seroconverted for anti-HEV IgG during the follow-up. This represent an incidence rate of 5.6 cases /100 patients-year (95% CI: 3.8%-7.5%). Among the 34 HEV seroconverted patients, in two (5.8%) HEV-RNA was amplified. Twenty-one patients (61.7%) presented clinical manifestation and/or changes in liver function test at the time of seroconversion. The more frequent clinical manifestations were: fever (11/21; 52.3%), digestive manifestation (12/21; 57.1%), diffuse abdominal pain (10/21; 47.6%) and asthenia (20/21; 95.2%). Among these patients, one (co-infected with Hepatitis B virus in liver cirrhosis stage) presented liver decompensation (ascites) at the moment of the HEV seroconversion. Interestingly, 10 (47.6%) of these patients experienced HIV viral blips during the HEV seroconversion.

Conclusions: HEV present a high prevalence and incidence in HIV infected patients. In the majority of patients, HEV infection curse as a symptomatic disease. In our study, HEV seroconversion was associated with HIV viral blips.

TUESDAY, FEBRUARY 24, 2015

Session P-01 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HPV Infections and Cancers

710 Factors Associated With Extensive Cervical Lesions Among HIV-Infected Women Screening for AIDS Clinical Trials Group (ACTG) Protocol A5282

Timothy J. Wilkin[1]; Roy Matining[2]; Vikrant Sahasrabuddhe[3]; Catherine Godfrey[4]; Thandie Lungu[5]; Mulindi Mwanahamuntu[6]; Ramesh Bhosale[7]; Scott Evans[2]; Robert W. Coombs[8]; Cynthia Firnhaber[9]

[1]Weill Cornell Medical College, New York, NY, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Cambridge, MA, US; [3]National Cancer Institute (NCI), Bethesda, MD, US; [4]Division of AIDS (DAIDS), NIAID, NIH, Bethesda, MD, US; [5]University of North Carolina Project–Malawi, Lilongwe, Malawi; [6]University Teaching Hospital, Lusaka, Zambia; [7]Byramjee Jeejeebhoy Medical College, Pune, India; [8]University of Washington, Seattle, WA, US; [9]University of Witswatersand, Johannesburg, South Africa

Background: 'Screen-and-treat' approaches for prevention of cervical cancer are used in many resource-constrained settings because of the challenges associated with cytology. Women are **screened** with: (1) visual inspection after acetic acid (VIA), or (2) testing for high-risk human papillomavirus (hrHPV), followed by **treatment** with cervical cryotherapy for those screening positive. However, women may have extensive cryotherapy-ineligible lesions that require excisional procedures. We explored factors associated with these lesions to inform broad implementation of screen and treat programs.

Methods: Cross-sectional study of HIV-infected women screening for A5282, a randomized clinical trial comparing the HPV screen and treat approach to a cytology-based strategy for prevention of cervical cancer. Participants were screened with colposcopy (visual inspection after acetic acid wash using magnification without biopsy), HPV testing (Abbott® hrHPV PCR assay), and cytology. Colposcopy results were categorized as no lesions, cryo-eligible lesions, and cryo-ineligible lesions according to WHO criteria. Participating sites included 8 in sub-Saharan Africa, 2 in India, 1 in Haiti, and 1 in Peru. Fisher's exact test was used to test for association.

Results: 907 women who screened for A5282 had complete colposcopy, hrHPV, and cytology results. The median age (years) was 37 [IQR 32, 42]; median CD4 (cells/mm^3) was 524 [IQR 386, 712]; 70% has plasma HIV-1 RNA <40 copies/mL. Cryo-ineligible lesions were not associated with CD4 count or plasma HIV-1 RNA. The prevalence of cryo-ineligible lesions was significantly higher in women with hrHPV than without (105/403, 26% vs. 44/504, 9%, $P<0.001$), and in those with abnormal cytology than with normal cytology (110/597, 18% vs. 39/310, 13%, $P=0.024$).

Summary of cervical cancer screening test results and cryo-eligibility among 907 HIV-infected women

	Screening Test		
Result	**colposcopy**	**hrHPV**	**cytology**
Screen negative	487 (54%)	504 (56%)	310 (34%)
Cryo-ineligible, N (%)	*N/A*	*44 (5%)*	*39 (4%)*
Screen positive, N (%)	420 (46%)	403 (44%)	597 (66%)
Cryo-ineligible, N (%)	*149 (16%)*	*105 (12%)*	*110 (12%)*

Colposcopy screen positive= lesions seen after acetic acid; Cytology screen positive=atypical squamous cells or greater; N/A=not applicable

Conclusions: Extensive cervical lesions that are not eligible for treatment with cryotherapy are relatively common (~1 in 6) among HIV-infected women and are not associated with immune suppression or lack of virological control. Adequate treatment for these lesions, such as loop electrosurgical excision procedure, should be readily available within 'screen-and-treat' implementation programs. Further studies are needed to define the optimal management of these lesions.

711 HIV Infection and Survival Among Women With Cervical Cancer in Botswana

Scott Dryden-Peterson[1]; Memory Bvochora-Nsingo[2]; Heluf Medhin[3]; Gita Suneja[4]; Aida Asmelash[5]; Malebogo Pusoentsi[3]; Anthony Russell[6]; Jason Efstathiou[6]; Bruce Chabner[6]; Shahin Lockman[1]

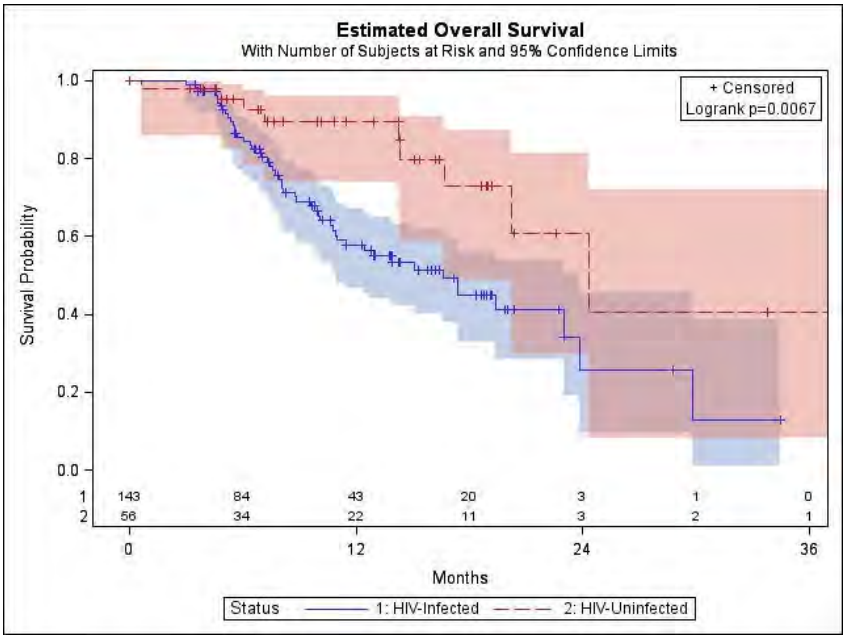
[1]Brigham and Women's Hospital, Harvard Medical School, Jamaica Plain, MA, US; [2]Gaborone Private Hospital, Gaborone, Botswana; [3]Botswana Ministry of Health, Gaborone, Botswana; [4]University of Utah, Salt Lake City, UT, US; [5]Botswana Harvard AIDS Institute, Gaborone, Botswana; [6]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

Background: Cervical cancer is the most common malignancy in African women and incidence has increased with expansion of ART coverage. We sought to prospectively evaluate the association between HIV-infection and survival of patients diagnosed with cervical cancer in a country with high HIV treatment coverage.

Methods: We enrolled sequential patients presenting for initial treatment of cervical cancer at two referral hospitals in Gaborone, Botswana from October 2010 through September 2014. Consenting patients were tested for HIV and their records were abstracted. Standard treatment included radiation (both external beam and brachytherapy) with concurrent cisplatin added for locally advanced cases. Patients were followed every 3 months for treatment outcome. Association between HIV infection and all-cause mortality was assessed using the logrank test and Cox proportional hazards modeling.

Results: A total of 215 women with cervical cancer were enrolled, including 146 (67.9%) HIV-infected, 58 (27.0%) HIV-uninfected, and 11 (5.1%) with unknown HIV status. Only 8 (3.7%) cancers were identified by screening and symptoms prompted diagnosis in remaining 207 (96.3%). HIV-infected women were younger than women without HIV— median age 41.3 and 57.6 years, respectively (P<0.001). At presentation with cancer, the median CD4 count for HIV-infected women was 406 cells/μL (IQR 283 - 550 cells/μL) and 86.8% were receiving ART (median duration 4.4 years). Sixty-eight (47.9%) of HIV-infected women and 22 (39.3%) of HIV-uninfected women presented with FIGO stage 3 or 4 cancer

(P=0.34). Fifty (35.0%) HIV-infected and 9 (16.1%) HIV-uninfected women died during follow-up. Of these 59 deaths, 47 (79.7%) were attributed to cancer and 1 (1.7%) to toxicity of treatment; cause of death was unknown for 11 (18.6%). Median survival for HIV-infected women was shorter than HIV-uninfected women, median 16.6 versus 24.3 months, respectively (P=0.007), see Figure. Findings were similar after adjustment for stage, with HIV-infection associated with increased mortality (HR 2.66, 95% CI 1.3 - 5.5, P=0.008). Advanced cancer stage was strongly predictive of mortality (P=0.002). Among women with HIV, CD4 cell count or ART duration was not associated with survival.



Conclusions: Despite ART, HIV-infection is associated with increased mortality among women with cervical cancer. Overall survival is poor among women with HIV-associated cervical cancer in Africa and further research is needed to understand factors contributing to excess mortality.

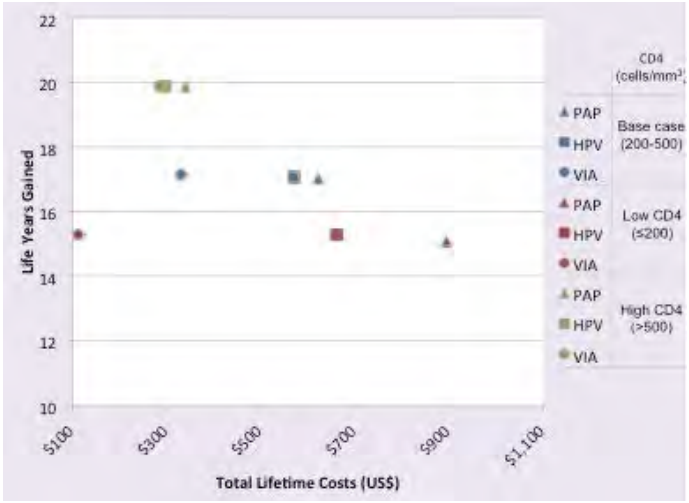
712 Potential Cost-Effectiveness of Cervical Cancer Screening of HIV-Positive Kenyan Women

Marita Mann; Joseph Babigumira; Louis Garrison; Michael Chung
University of Washington, Seattle, WA, US

Background: As antiretroviral therapy is scaled up in Africa, HIV-positive women are living longer and increasingly likely to die from cervical cancer. Cervical cancer screening methods used in these settings include Papanicolaou smear (Pap), visual inspection with acetic acid (VIA), and human papillomavirus testing (HPV). Our objective was to assess the cost-effectiveness of these methods among HIV-positive women.

Methods: The cost-effectiveness analysis was based on a trial of 500 HIV-positive women who underwent VIA, Pap smear, HPV, and gold-standard colonoscopy-directed biopsy at the Coptic Hope Center in Nairobi, Kenya. We used a decision tree to assess overall cost-effectiveness comparing Pap, VIA, and HPV. A Markov model consisting of 7 disease states projected life expectancy and costs following each strategy. The base case analysis included those with CD4 count 200-500 cells/mm^3. We additionally modeled patients with low and high CD4 counts. We addressed the impact of parameter uncertainty using univariate and probabilistic multivariate sensitivity analysis. Costs included direct and indirect medical and non-medical costs from a semi-societal perspective.

Results: VIA had lowest cost and highest life expectancy (due to reduced loss-to-follow-up) ($331, 17.2 LYs), followed by HPV ($563, 17.1 LYs), Pap ($622, 17.1 LYs) (Figure 1). CD4 level did not affect this rank order, though VIA at low CD4 showed the lowest cost ($111, 15.3 LY), while VIA at high CD4 produced most health gains ($285, 19.9 LY) [ICER: $37/LY]. Costs were sensitive to prevalence of cancer, sensitivity, age, and cost of cancer. Life expectancy was sensitive to age at screening. Results were robust to probabilistic sensitivity analysis.



Conclusions: While VIA had lower sensitivity (62.7%), its low cost ($2.05) projected it to have the lowest lifetime cost while producing the highest health gains. HPV testing was the most sensitive test (83.6%); however, its relatively high cost ($10.34) made VIA a better choice. Low risk treatment and high cervical cancer cost caused screening cost to drive the model. Screening women with high CD4 is particularly cost-effective because longer life expectancy leads to higher health gains with less cost variation. Costing and time motion studies are currently being undertaken in Kenya to more accurately represent costs for improved analysis and results.

713 Anal High-Risk Human Papillomavirus (HPV) Infection Among HIV-Infected MSM in the SUN Study, 2004-2011

Pragna Patel[1]; Tim Bush[1]; Erna Kojic[2]; Lois Conley[1]; Elizabeth Unger[1]; Teresa Darragh[3]; Keith Henry[4]; John Hammer[5]; Nur Onen[6]; Joel Palefsky[3]

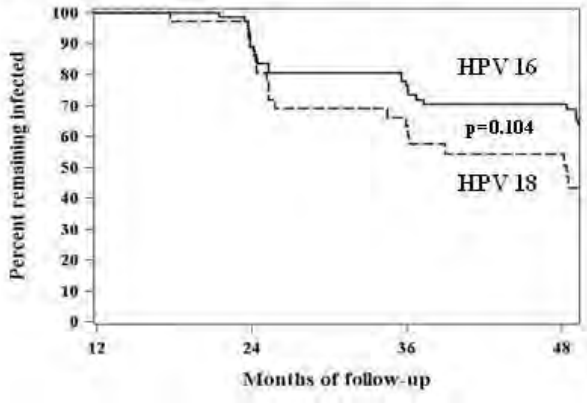
[1]CDC, Atlanta, GA, US; [2]Brown University, Providence, RI, US; [3]University of California San Francisco, San Francisco, CA, US; [4]University of Minnesota, Minneapolis, MN, US; [5]Denver Infectious Diseases Consultants, Denver, CO, US; [6]Washington University School of Medicine, St. Louis, MO, US

Background: Incidence and clearance of anal high-risk HPV (HR-HPV) infection in HIV-infected men who have sex with men (MSM) have not been well characterized. These dynamics may have implications for vaccine strategies to reduce anal cancer burden.

Methods: The SUN Study is a prospective observational cohort of HIV-infected patients receiving care in four U.S. cities. Among MSM, we evaluated the baseline prevalence of HPV types 16 and 18 at the anus and incidence and clearance annually over 48 months using Kaplan-Meier survival analysis. For men with prevalent HPV 16 or HPV 18, we defined clearance as two consecutive visits where the respective HPV type was undetected. We assessed the associations of prevalent and incident infection, and clearance of prevalent infection, with selected baseline behavioral and clinical characteristics.

Results: In 403 MSM, the median age was 42 years; 78% were prescribed HAART; median CD4 cell count was 454 cells/mm^3; and 74% had an undetectable viral load. The prevalence of HPV 16 was 38% (n=152) and HPV 18 was 24% (n=97) (p=0.193); 10% (n=42) were co-infected with both HPV types. Men who injected drugs were more likely to be infected with prevalent HPV 16 (53% vs. 36%, p=0.024), while men with rectal *Neisseria gonorrhea* infection (67% vs. 24%, p=0.009), CD4 cell count < 500 cells/mm^3 (29% vs. 17%, p=0.004), and ≥ 4 sex partners during the 6 months before baseline (33% vs. 21%, p=0.012) were more likely to be infected with prevalent HPV 18. Over 48 months, the incidence of HPV 16 was 23% (95% confidence interval (CI): 18%-30%) and of HPV 18 was 13% (95% CI: 9%-17%). Five percent (n=8) had both incident HPV 16 and 18 detected. Anal sex in the 6 months before baseline (31% vs. 14%, P=0.006) and consuming alcohol in 30 days before baseline (25% vs. 10%, p=0.038) were associated with HPV 16; marijuana use in 6 months before baseline was associated with HPV 18 (20% vs. 10%, p=0.021). At 48 months, 26% (95% CI: 18%-36%) cleared prevalent HPV 16 and 50% (95% CI: 38%-64%) cleared HPV 18 (Figure). In MSM with vs without persistent HPV 16 and 18, squamous intraepithelial lesions were detected in 56% vs 37% (p=0.006), and 68% vs 38% (p=0.003), respectively. MSM who reported ever using methamphetamine vs no use were less likely to clear HPV 16 (24% vs 46%, p=0.039).

Figure. Clearance of high-risk anal HPV type 16 and type 18 infection among HIV-infected MSM



Conclusions: Among HIV-infected MSM with a prevalent HR-HPV infection, 26% with HPV 16 and 50% with HPV 18 cleared by 48 months. MSM using methamphetamine vs no use may be at higher risk for anal dysplasia and cancer.

714 Long-Term Effectiveness of Electrocautery Ablation of HGAIN in HIV-Infected MSM

Joaquin Burgos[1]; Adria Curran[1]; Natalia Tallada[1]; Ana Guelar[2]; Jordi Navarro[1]; Stefania Landolfi[1]; Judith Villar[2]; Manel Crespo[1]; Esteve Ribera[1]; Vicenç Falco[1]

[1]University Hospital Vall d'Hebron, Barcelona, Spain; [2]University Hospital del Mar, Barcelona, Spain

Background: HIV-infected men who have sex with men (MSM) are at risk for high-grade anal intraepithelial neoplasia (HGAIN) and anal cancer. The goal of the anal screening programs is to identify these precancerous lesions in order to ablating them and hence reducing the incidence of anal cancer. Although electrocautery (EC) is one of the main treatment options, there are scarce data regarding its efficacy. The aim of the study was to evaluate the effectiveness of EC for the treatment of HGAIN.

Methods: Observational study of HIV-infected MSM diagnosed with HGAIN in our screening program treated with EC ablation. The effectiveness of treatment was evaluated for each cycle (including 3-5 electrocautery sessions) and at the end of the full (including all cycles for each patient). Response was evaluated according to anal biopsy samples obtained 2-3 months after treatment. Complete response was defined as resolution of HGAIN and partial response as regression to low-grade AIN. Recurrence was considerate as biopsy-proven HGAIN in the follow-up after the treatment. The effectiveness was evaluated using an on-treatment analysis. Patients who interrupted treatments or were lost to follow-up were censured.

Results: From May 2009 to September 2014, 111 (19.7%) patients out of 564 who underwent anal cancer screening had HGAIN. The treatment effectiveness was evaluated in 73 patients. A complete response was observed in 21 (28.8%; 95% CI, 19.6-40), a partial response in 26 (35.6%; 95% CI, 25.6-47.1) and persistence in 26 (35.6%; 95% CI, 25.6-47.1). In 85% of the patients treated successfully, only one cycle of EC was required.

The effectiveness of the 96 evaluable cycles of treatment was: 22% complete response, 27% partial response and 51% non response. No patients developed serious adverse events after EC. No differences regarding HIV infection, sexual behavior or anal dysplasia characteristics were observed between responders and no responders.

After a mean follow-up of 18.3 months, 10 of 47 patients (21.3%; 95% CI, 12-35) with a complete or partial response developed recurrent HGAIN with a mean time to recurrence of 39 (95% CI, 30.7-47.3) months. No patient progressed to invasive anal cancer during the study period.

Conclusions: Although EC is the standard of care for treating anal dysplasia, almost 50% of patients with HGAIN in our study did not respond or relapse to EC. New treatment strategies are necessary to optime the management of patients with anal dysplasia.

715 Survival and Treatment Trends for Squamous Cell Carcinoma of the Anus in HIV Infection

Robert A. Pitts; Stephen Goldstone; Keith Sigel; Michael M. Gaisa; Carlie Sigel; Juan Wisnivesky
Icahn School of Medicine at Mount Sinai, New York, NY, US

Background: HIV seropositive (HIV+) patients are at increased risk of squamous cell carcinoma of the anus (SCCA). Howevere, there are limited data regarding antiretroviral era survival and treatment trends for HIV+ patients with SCCA.

Methods: We used data from the Surveillance, Epidemiology, and End Results (SEER) registry linked to Medicare claims to evaluate outcomes among a cohort of male HIV+ and HIV- patients diagnosed with SCCA from 1997 to 2009. Outcomes included all-cause and anal cancer-specific mortality, colostomy placement, and SCCA recurrence. Kaplan-Meier methods were employed to compare outcomes (among the whole cohort and then stratified by cancer stage) by HIV status. We developed Cox regression models to adjust for age, race/ethnicity, modified Charlson comorbidity score, cancer stage and diagnosis year. Initial courses of treatment (surgery, radiotherapy, and chemotherapy) were also identified and compared by HIV status and SCCA stage.

Results: 1,000 male patients with incident SCCA were included in our cohort, of whom 370 were HIV+. When compared to HIV- patients, HIV+ subjects were younger (median age 48, $p<0.05$), had lower comorbidity scores ($p<0.05$), and were diagnosed with earlier stage cancers ($p=0.03$). Median survival in HIV+ SCCA patients ranged from 95 months (95% CI: 79 - 125) for stage 1 to 23 months (95% CI: 10 - 56) for stage IV. For early stage SCCA, we observed no difference in the pathologic depth of carcinoma invasion by HIV status ($p=0.5$). However, initial treatment varied by HIV status and SCCA stage (Table 1). In adjusted analyses, HIV patients had worse overall survival (HR 1.5, %CI: 1.2 - 2.0), but no difference in anal cancer-specific survival, colostomy placement or cancer recurrence.

Table 1: Treatment Comparison by HIV Status and SCCA Stage.

	Stage I/II			Stage III/IV		
Initial treatment	HIV- (%)	HIV+ (%)	P-value	HIV- (%)	HIV+ (%)	P-value
Surgery only	103 (19)	66 (21)		5 (5)	4 (9)	
Surgery/Chemo	2 (0)	4 (1)		0	0	
Surgery/Chemo/Radiation	123 (23)	97 (30)		15 (16)	16 (34)	
Surgery/Radiation	40 (7)	49 (15)		15 (16)	6 (12)	
Radiation only	79 (15)	29 (9)		18 (19)	4 (9)	
Chemo/Radiation	163 (30)	66 (21)		33 (36)	17 (36)	
Chemo only	5 (1)	0		1 (1)	0	
No treatment	24 (5)	10 (3)		6 (7)	0	
Total	539	321	p<0.001	93	47	0.08

Conclusions: In our population-based cohort, we found that HIV+ patients with SCCA presented with earlier stage cancers (possibly related to anal cancer screening) and had worse overall survival than HIV- patients. SCCA-specific survival did not differ by HIV status despite discordance in initial treatment, suggesting that overall survival differences were related to HIV-related sources of mortality.

716 Oral HPV Shedding and Warts After Starting Antiretroviral Therapy: ACTG Protocol A5272

Caroline H. Shiboski[1]; Anthony Lee[2]; Jennifer Webster-Cyriaque[3]; Huichao Chen[2]; Malcolm John[1]; Raphael J. Landovitz[4]; Mark Jacobson[1]
Oral HIV/AIDS Research Alliance and the AIDS Clinical Trial Group
[1]*University of California San Francisco, San Francisco, CA, US;* [2]*Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US;* [3]*University of North Carolina, Chapel Hill, NC, US;* [4]*University of California Los Angeles, Los Angeles, CA, US*

Background: Previous studies have suggested an increase in the incidence of oral warts following antiretroviral therapy (ART) initiation. In addition, there are recent reports of an increasing incidence of human papilloma virus(HPV)-related oral malignancies among the US population living with HIV infection, despite the widespread availability of ART for almost two decades. Therefore, we sought to explore whether ART initiation among treatment-naïve HIV-positive adults was followed by an increase in oral wart incidence or a decrease in oral HPV shedding.

Methods: AIDS Clinical Trial Group protocol A5272 was a prospective, observational study of HIV-1 infected ART naïve adults who were initiating ART. Endpoints included detection of HPV DNA in throat washes and diagnosis of oral warts measured at two time points prior to ART initiation as well as at 16 and 24 weeks after ART initiation. An oral exam for warts was also performed at 48 weeks.

Results: Among 500 participants enrolled, 390 (78%) were men and 110 (22%) women. Among the 396 participants who had evaluable throat wash HPV DNA results from at least one time point before initiating ART and again after 16 or 24 weeks of ART, 76 (19%) had at least one subtype of HPV DNA present before starting ART and 100 (25%) had at least one subtype present after 16 or 24 weeks of ART. In addition, after 16 or 24 weeks of ART, 80 (20%) had a new HPV subtype present in throat wash that was not identified in the specimens obtained before initiating ART. Also, among those with HPV DNA present before initiating ART, 48 (63%) cleared at least one of the prevalent subtypes during follow-up, while 17 (22%) persisted in shedding at least one of the prevalent subtypes. Oral warts were detected in 3% of participants at study entry. Among those who did not have any warts at entry, only 2.5% had acquired one or more warts by 16, 24, or 48 weeks of ART.

Conclusions: Both prevalence and incidence of oral warts were low. However, high proportion of participants shed HPV from the oral cavity both before and after ART initiation. Furthermore, HPV subtypes absent at baseline were detected after ART initiation. The results of this study suggest that effective immune control of HPV replication in the oral cavity is not reconstituted by ART in HIV-infected patients during the first 24 weeks of therapy. The prevalence of HPV-associated oral malignancies may continue to increase in the modern ART era.

Supported by NIH/NIAID/NIDCR Cooperative Agreement U01AI068636

717 Excess Risk of Rectal Squamous Cell Carcinoma in HIV-Infected Persons

Anna E. Coghill; Meredith S. Shiels; Eric A. Engels
National Cancer Institute, Rockville, MD, US

Background: The majority of rectal cancers diagnosed in the US are adenocarcinomas. Rectal squamous cell carcinoma (RSCC) is rare, representing only 1-2% of rectal tumors in the general population. However, we observed in preliminary analyses that ~30% of rectal tumors in HIV-infected persons were RSCC. We therefore explored whether HIV-infected persons have a significantly higher risk of RSCC.

Methods: We utilized the HIV/AIDS Cancer Match, a linkage of US HIV and cancer registries (1991-2010), to ascertain cases of rectal (squamous and non-squamous) and anal cancer. We calculated standardized incidence ratios (SIRs) comparing the number of observed cases in HIV-infected persons to the number expected based on general population rates. To examine whether RSCC in HIV-infected persons represents systematically misclassified anal cancer rather than a distinct entity, investigators reviewed case notes for a subset of rectal and anal tumors.

Results: Among 1,194 HIV-infected persons, 89 cases of RSCC were diagnosed. HIV-infected persons had an elevated risk of RSCC (SIR=28.9; 95% CI 23.2-35.6), similar to that reported for anal cancer (SIR=32.3; 95% CI 30.0-34.6). The largest RSCC excess occurred in MSM (SIR=61.2; 95% CI 47.8-77.0). In contrast, non-squamous rectal cancer risk was not elevated among HIV-infected persons (SIR=0.88; 95% CI 0.74-1.04). Approximately 33% of RSCC cases were determined to be misclassified anal cancer cases after review, but misclassification was non-differential (HIV-infected: 34.5%; HIV-uninfected: 33.3%).

TABLE 1. Standardized Incidence Ratios (SIRs) comparing the number of observed cases in HIV-infected persons to the number of expected cases in the general population, according to cancer type and covariate strata

	Anal Cancer (N=766)		Rectal SCC (N=89)		Rectal Non-SCC (N=135)		Colon Cancer (N=197)	
	Observed	SIR (95% CI)	Observed	SIR (95% CI)	Observed	SIR (95% CI)	Observed	SIR (95% CI)
OVERALL	766	32.3 (30.0-34.6)	89	28.9 (23.2-35.6)	135	0.88 (0.74-1.04)	199	0.64 (0.55-0.73)
Risk Categories								
MSM	577	58.3 (53.6-63.2)	71	61.2 (47.8-77.2)	58	0.87 (0.66-1.13)	63	0.53 (0.41-0.68)
Non-MSM Male IDU	50	12.4 (9.23-16.4)	4	9.09 (2.48-23.4)	27	1.01 (0.66-1.46)	29	0.55 (0.37-0.79)
Female IDU	21	13.0 (8.02-19.8)	3	11.5 (2.38-33.7)	8	1.03 (0.45-2.03)	14	0.73 (0.40-1.23)
Male Heterosexual	27	14.4 (9.46-20.9)	2	8.7 (1.05-31.4)	12	0.95 (0.49-1.65)	23	0.83 (0.53-124)
Female Heterosexual	32	14.8 (10.1-20.8)	5	11.9 (3.87-27.8)	13	1.12 (0.60-1.92)	25	0.83 (0.54-1.22)
Male Other	2	22.2 (2.7-80.3)	0	0 (0-368)	1	1.23 (0.03-6.88)	0	0 (0-2.26)
Female Other	1	20.0 (0.51-111)	0	0 (0-368)	1	3.57 (0.09-19.9)	3	3.61 (0.75-10.6)
Male Unknown	42	14.5 (10.5-19.6)	4	12.1 (3.30-31.0)	11	0.54 (0.27-0.96)	24	0.56 (0.36-0.83)
Female Unknown	14	12.4 (6.8-20.8)	0	0 (0-16.8)	4	0.60 (0.16-1.54)	18	1.01 (0.60-1.59)
Age (years)								
<30	17	89.5 (52.1-143)	3	150 (30.9-438)	0	0 (0-4.1)	2	1.32 (0.16-4.78)
30-39	184	49.3 (42.5-57.0)	25	56.8 (36.8-83.9)	26	2.28 (1.49-3.34)	19	0.88 (0.53-1.38)
40-49	358	33.0 (29.7-36.6)	43	30.5 (22.1-41.1)	49	1.01 (0.75-1.33)	58	0.68 (0.52-0.88)
50-59	156	23.5 (19.9-27.4)	16	17.6 (10.1-28.6)	39	0.66 (0.47-0.90)	60	0.52 (0.39-0.66)
60-69	45	24.9 (18.1-33.3)	1	4.35 (0.11-24.2)	16	0.64 (0.37-1.04)	43	0.69 (0.50-0.93)
70+	6	11.3 (1.45-24.6)	1	12.5 (0.32-69.7)	5	0.61 (0.2-1.41)	17	0.69 (0.40-1.10)
Time Relative to AIDS								
HIV Only	81	10.5 (8.30-13.0)	16	17.6 (10.1-28.6)	35	0.74 (0.52-1.03)	54	0.56 (0.42-0.73)
0-3 mo. after AIDS	26	52.0 (34.0-76.2)	5	62.5 (20.3-145)	6	1.89 (0.69-4.12)	13	1.91 (1.02-3.27)
4-27 mo. after AIDS	78	27.9 (22.0-34.8)	12	28.6 (14.8-49.9)	17	0.97 (0.56-1.55)	22	0.59 (0.37-0.90)
28-60 mo. after AIDS	136	36.4 (30.5-43.0)	16	29.6 (16.9-48.1)	22	0.93 (0.58-1.40)	43	0.87 (0.63-1.18)
60+ mo. after AIDS	445	49.7 (45.2-54.6)	40	35.1 (25.1-47.8)	55	0.89 (0.67-1.16)	67	0.59 (0.46-0.75)
Race/Ethnicity								
White	417	52.3 (47.4-57.6)	47	49.0 (36.0-65.1)	51	0.89 (0.66-1.17)	52	0.52 (0.39-0.69)
Black	249	18.8 (16.6-21.3)	24	13.3 (8.5-19.8)	70	0.94 (0.73-1.19)	113	0.65 (0.53-0.78)
Hispanic	86	33.9 (27.1-41.8)	16	48.5 (27.7-78.7)	11	0.50 (0.25-0.90)	32	0.85 (0.58-1.20)

Abbreviations: SCC (squamous cell carcinoma), MSM (men who have sex with men), IDU (injection drug user)

Conclusions: HIV is associated with a substantial excess risk of RSCC. The pattern of excess risk is similar to that observed for anal cancer, an HPV-associated tumor. Although a portion of cases may be misclassified anal cancer, the amount of misclassification was too small to explain the excess. RSCC in HIV-infected persons could represent a previously unrecognized and etiologically distinct subset of rectal tumors, with the particularly high risk in MSM pointing to involvement of a sexually transmitted infectious agent such as HPV.

WEDNESDAY, FEBRUARY 25, 2015

Session P-02 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

AIDS-Related Cancers: Lymphoma and KS

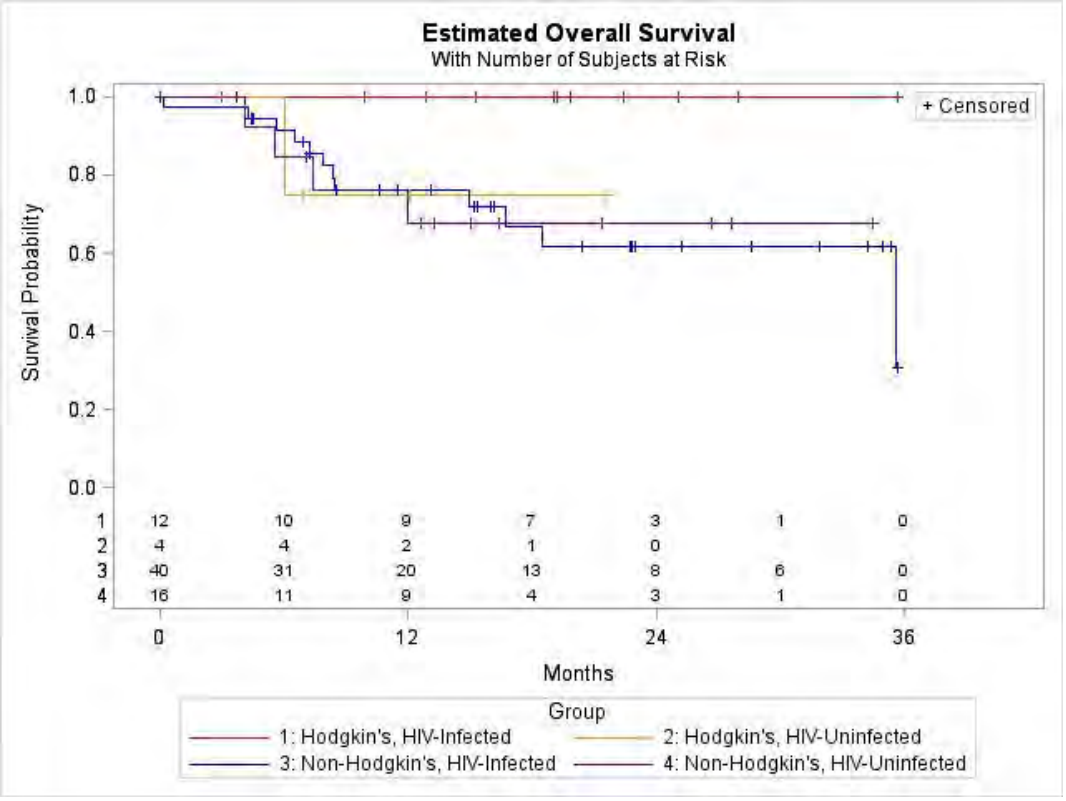
718 Incidence and Outcomes of HIV-Associated Lymphomas in Botswana

Michael G. Milligan[1]; Elizabeth Bigger[3]; Musimar Zola[7]; Mukendi Kayembe[6]; Heluf Medhin[5]; Gita Suneja[4]; Shahin Lockman[2]; Jeremy Abramson[3]; Bruce Chabner[3]; Scott Dryden-Peterson[2]
[1]Harvard Medical School, Brookline, MA, US; [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [4]University of Utah, Salt Lake City, UT, US; [5]Botswana Ministry of Health, Gaborone, Botswana; [6]Botswana National Health Laboratory, Gaborone, Botswana; [7]Princess Marina Hospital, Gaborone, Botswana

Background: In the US and Europe, lymphoma incidence fell with introduction of ART. However, incidence of non-Hodgkin's (NHL) and Hodgkin's lymphoma (HL) has risen despite excellent ART access in Botswana. We sought to better understand the paradoxical rise in incidence and assess the treatment and outcomes of patients with NHL and HL in Botswana.

Methods: We enrolled all consenting adults treated for lymphoma between 10/2010 and 9/2014 at two referral hospitals in Gaborone, Botswana. Standard treatment included 6 cycles of CHOP (recently with rituximab) for NHL and 6 cycles of ABVD for HL. ART-naïve HIV-infected patients or those who started ART within 6 months of lymphoma diagnosis were categorized as off ART. Exact methods were used for categorical measures and survival was assessed using Cox modeling adjusted for lymphoma type (NHL or HD).

Results: Seventy-two patients were enrolled (56 NHL, 16 HL) and followed for a median 12.9 months. Fifty-two (72%) patients were HIV-infected and 20 (28%) were HIV-uninfected. The median age of HIV-infected and HIV-uninfected patients was 37 and 52 years with NHL (P=0.059) and 40 and 32 years with HL (P=0.38), respectively. Among HIV-infected, 42% of lymphomas were diagnosed in patients on ART (median duration 2.6 years), with median CD4 count of 255 cells/μL (IQR 147-390 cells/μL) for NHL and 401 cells/μL (IQR 311-525 cells/μL) for HL. In those patients off ART, 41% were eligible to have been initiated on ART by CD4 count alone (≤ 250 cells/μL). Fifty percent of NHL and 36% of HL patients presented at advanced stages (Ann Arbor stage III or IV). Chemotherapy records were analyzed in 43 (60%) cases and all patients were started on standard treatment regimens. Treatment modifications were common and due to toxicity (22 instances) and chemotherapy stock out (5 instances). Sixteen NHL patients (28%) and 1 HL patient (6%) died during follow-up. The one-year survival was 74% (95% CI 58 – 84%) for NHL and 93% (95% CI 59-99%) for HL. While power was low, no significant differences were detected in stage at presentation (p=0.76), treatment modification (p=0.60), or survival (HR 0.76, 95% CI 0.26-2.2) by HIV status.



Conclusions: Despite ART coverage exceeding 90% by government estimates, the majority of lymphomas were diagnosed in patients off ART with relatively high CD4 cell counts. Persistently high incidence may be related to low CD4 thresholds for ART eligibility. HIV-infection was not associated with reduced survival, although sample size was limited.

719 CHOP Is Feasible for HIV-Associated Lymphoma in the ART Era in Malawi

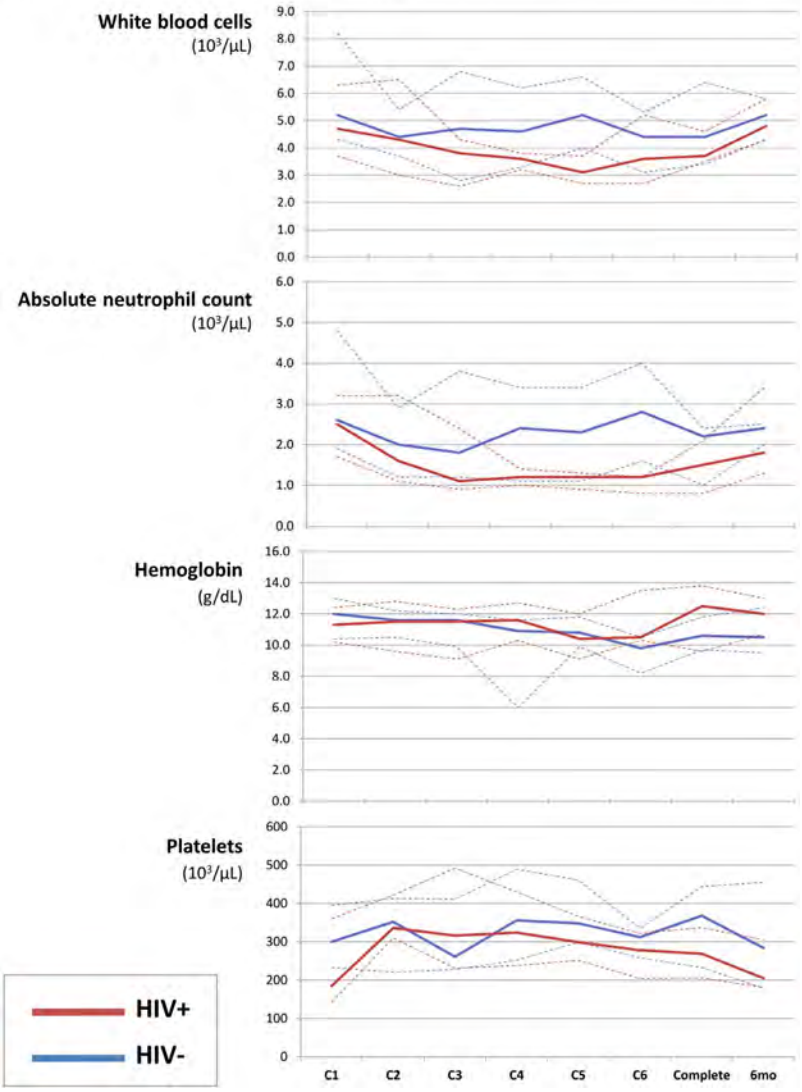
Satish Gopal[2]; Yuri Fedoriw[1]; Agnes Moses[2]; Nathan Montgomery[1]; Wongani Kaimila[2]; Coxcilly Kampani[2]; Robert Krysiak[2]; Kristy Richards[1]; Thomas Shea[1]; George Liomba[2]
[1]*University of North Carolina, Chapel Hill, NC, US;* [2]*University of North Carolina Project–Malawi, Lilongwe, Malawi*

Background: Although it is the standard treatment throughout the region, there is no prospective study describing use of CHOP for lymphoma patients in sub-Saharan Africa in the antiretroviral therapy (ART) era.

Methods: We describe a prospective longitudinal cohort of adult lymphoma patients receiving CHOP at a national teaching hospital in Malawi between June 2013 and August 2014. Chemotherapy and supportive care are given using standardized monitoring and dose adjustment, and HIV+ patients receive concurrent ART.

Results: Thirty-five patients (34 non-Hodgkin, 1 Hodgkin; 19 HIV+, 16 HIV-) were treated with CHOP, with median age 48 years (range 22-77), 26 being (74%) male, and 20 (57%) with stage III/IV disease. Clinical characteristics were overall similar between HIV+ and HIV- patients. Seventeen HIV+ patients (90%) were on ART for a median 18.9 months (range 0.2-98.8) at lymphoma diagnosis. Median CD4 count among HIV+ patients was 138 cells/μL (range 32-1,013), and 10 (53%) had suppressed HIV RNA. HIV+ patients experienced greater leukopenia and neutropenia during chemotherapy, with similar hemoglobin and platelet count levels (Figure). However, median absolute neutrophil count (ANC) remained ≥1x10^3/μL during treatment even for HIV+ individuals. Among HIV+ patients completing chemotherapy, white blood cell (WBC) and ANC levels returned to values similar to HIV- patients by six months. Grade 3/4 neutropenia occurred in more HIV+ than HIV- patients (83% vs 31%, p=0.015). Of 32 grade 3/4 neutropenia events, 29 were grade 3 and three were grade 4. For HIV+ patients, median CD4 count increased to 180 cells/μL (range 44-369) at six months. Cumulative dose and dose intensity were similar for HIV+ and HIV- patients, as assessed by CHOP cycles per patient (median 5 HIV+ vs 4 HIV-, p=0.43), days between cycles (median 21 vs 21, p=0.15), cyclophosphamide dose (mg/m2) per cycle (median 723 vs 710, p=0.48), and doxorubicin dose (mg/m2) per cycle (median 49 vs 49, p=0.38). Eighteen patients (60%) received <6 CHOP cycles (53% HIV+ vs 67% HIV-, p=0.71), with reasons being death (n=11, 4 HIV+, 7 HIV-), toxicity (n=4, 3 HIV+, 1 HIV-), social barriers (n=2, 1 HIV+, 1 HIV-), and disease progression (n=1, HIV-).

Figure. Peripheral blood counts and interquartile ranges during CHOP chemotherapy in Lilongwe, Malawi.



Conclusions: In the current ART era, CHOP can be safe, effective, and feasible for lymphoma patients in Malawi with and without HIV who receive standardized monitoring, dose adjustment, and supportive care.

720 Chronic Hepatitis B and C Infection and Risk for Non-Hodgkin Lymphoma in HIV-Infected Patients

Heiner C. Bucher
On behalf of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord
University Hospital Basel, Basel, Switzerland

Background: There is growing evidence that chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is associated with an increased risk of non-Hodgkin lymphoma (NHL) in the HIV-negative population. NHL continues to be one of the most common AIDS defining events even in the presence of antiretroviral therapy (ART). It is unclear whether chronic infection with HBV and HCV promotes NHL in HIV infection.

Methods: Using data from COHERE, ART-naïve individuals with no prior NHL diagnoses were followed from the latest of 1st January 2000 or entry into study cohort until NHL diagnosis, death, loss to follow up or 1st January 2013. Time periods during which patients were ART-naïve and ART-experienced were analysed separately due to time-dependent confounding. The association between time-updated chronic HBV (2 positive HBsAg measurements >6 months apart) and HCV (detectable HCV RNA or positive HCV Ab if HCV RNA unavailable) infection and NHL was assessed using Cox models with adjustment for age, gender, iv-drug use, HIV RNA, CD4 cell count and study cohort. Inverse probability of censoring weights were used to adjust for informative censoring due to death, starting ART or loss to follow up.

Results: We included 52,479 ART-naïve patients (1339 (3.3%) with HBV and 7506 (18.7%) with HCV; median follow up 13 months while ART-naïve), of whom 40,219 went on to start ART (1255 (3.1%) with HBV and 5481 (13.6%) with HCV; median additional follow up 50 months). Of patients with chronic HBV, 89% received an HBV-active ART; of patients with HCV, 15% were treated for HCV. During follow up, 252 ART-naïve and 310 ART-treated patients developed NHL, with incidence rates per 100,000 person-years of 219 and 168, respectively. In ART-naïve patients, no association was found between chronic HBV (HR=1.33; 95% CI 0.69, 2.57) and HCV infection (HR=0.67; 0.40, 1.12) with NHL. In ART-treated patients, those with chronic HBV (HR=1.75; 1.08, 2.83) and HCV (HR=1.73; 1.21, 2.46) were at increased risk of NHL. NHL occurred at low CD4 counts, particularly in HBV+ patients (see table).

Table: Patient characteristics at baseline and during follow up.

Characteristics	Patients with chronic HBV	Patients with HCV	Total
At time of HIV infection or inclusion	n=1339	n=7506	n=52,479
Female gender, %	19	24	22
Caucasian ethnicity, %	27	40	37
HIV transmission via IDU, %	12	56	10
Median age, years	36	36	35
Median HIV RNA, log_{10} copies/ml	4.7	4.5	4.6
Median CD4 cell count, cells/mm^3	320	380	380
At time of starting ART	n=1255	n=5481	n=40,219
Median HIV RNA, log_{10} copies/ml	4.9	4.8	4.9
Median CD4 cell count, cells/mm^3	240	230	247
At time of NHL diagnosis (in ART-naïve patients)	n=10	n=36	n=252
Median HIV RNA, log_{10} copies/ml	5.1	4.6	4.8
Median CD4 cell count, cells/mm^3	115	246	206
At time of NHL diagnosis (in ART-treated patients)	n=18	n=54	n=310
Median HIV RNA, log_{10} copies/ml	2.8	2.5	1.8
Median CD4 cell count, cells/mm^3	136	231	236

Conclusions: Chronic infection with HBV and HCV is associated with an increased risk of NHL in HIV-infected patients on ART. The higher risk for NHL represents an additional reason for improving prevention, diagnosis and management of viral hepatitis infections and early access to interferon free agents for HCV treatment in particular for HIV-infected patients with poor immune recovery.

721 HIV-Associated Kaposi Sarcoma Treated With Chemotherapy and ART in Rural Malawi

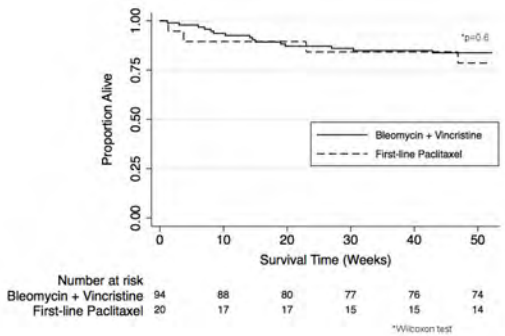
Michael E. Herce[1]; Noel Kalanga[2]; Jonathan T. Crocker[2]; Emily B. Wroe[2]; James W. Keck[2]; Felix D. Chingoli[3]; Satish Gopal[1]; Junior Bazile[2]; Jason A. Beste[2]; Jonas Rigodon[2]

[1]University of North Carolina, Chapel Hill, NC, US; [2]Partners In Health, Neno, Malawi; [3]Ministry of Health of the Republic of Malawi, Neno, Malawi

Background: HIV-associated Kaposi sarcoma (HIV-KS) is the most common cancer in Malawi. In 2008, the non-governmental organization, Partners In Health, and the Ministry of Health established the Neno Kaposi Sarcoma Clinic (NKSC) to treat HIV-KS in Neno district, one of Malawi's most rural districts. We hypothesized that a NKSC service delivery model using protocol-guided chemotherapy, integrated ART, and psychosocial support provided by community health workers would achieve excellent clinical outcomes at 12 months.

Methods: We conducted a retrospective cohort study using routinely collected clinical data from 114 adult NKSC patients initiating treatment between March 2008 and February 2012. Inclusion criteria were: documented HIV infection; ART receipt; KS diagnosed clinically or by histopathology; no prior combination chemotherapy treatment; and receipt of ≥1 chemotherapy cycle in the NKSC.

Results: At enrollment 97% of patients (n/N= 103/106) had advanced HIV-KS (stage T1). Most patients were male (n/N= 85/114, 75%) with median age 36 years (interquartile range, IQR: 29–42). Patients started ART a median of 77 days prior to chemotherapy (IQR: 36–252), with 97% (n/N= 105/108) receiving nevirapine/lamivudine/stavudine. Following standardized protocols, we treated 20 patients (18%) with first-line paclitaxel and 94 patients (82%) with bleomycin plus vincristine (BV). Of the 94 BV patients, 24 (26%) failed to respond to BV requiring change to second-line paclitaxel. A DAIDS grade 3/4 adverse event occurred in 29% of patients (n/N= 30/102). Neutropenia was the most common grade 3/4 event (n/N= 17/102, 17%). Twelve months after chemotherapy initiation, 83% of patients (95% CI: 74–89%) were alive, including 88 (77%) retained in care. Overall survival (OS) at 12 months did not differ by initial chemotherapy regimen (p=0.6). Among patients with T1 disease, low body mass index (BMI) (adjusted hazard ratio, aHR=4.10, 95% CI: 1.06–15.89) and 1 g/dL decrease in baseline hemoglobin (aHR=1.52, 95% CI: 1.03–2.25) were associated with increased rate of death or loss to follow-up at 12 months.



Kaplan-Meier survival estimates: 12-month overall survival in the Neno Kaposi Sarcoma Clinic stratified by initial chemotherapy regimen (Bleomycin plus Vincristine vs. First-line Paclitaxel; N=114).

Conclusions: The NKSC model resulted in infrequent adverse events, low loss to follow-up, and excellent OS. Our results suggest it is safe, effective, and feasible to provide standard-of-care chemotherapy regimens from the developed world, integrated with ART, to treat HIV-KS in rural Malawi. Baseline BMI and hemoglobin may represent important patient characteristics associated with HIV-KS survival in rural sub-Saharan Africa.

722 High Mobility Group Box 1 (HMGB1) and HIV-Associated Kaposi Sarcoma in Africa

Helen Byakwaga[1]; Peter W. Hunt[3]; Miriam O. Laker-Oketta[2]; Albert R. Davalos[6]; Conrad Muzoora[1]; David V. Glidden[3]; A. Rain Mocello[3]; David R. Bangsberg[4]; Edward Mbidde[5]; Jeffrey N. Martin[3]

[1]Mbarara University of Science and Technology, Mbarara, Uganda; [2]Infectious Diseases Institute, Kampala, Uganda; [3]University of California San Francisco, San Francisco, CA, US; [4]Massachusetts General Hospital, Center for Global Health, Harvard Medical School, Boston, MA, US; [5]Uganda Virus Research Institute, Entebbe, Uganda; [6]Buck Institute for Research on Aging, Novato, CA, US

Background: The high mobility group box 1 (HMGB1) protein, a host transcriptional regulator that promotes cell proliferation and is actively secreted by senescent cells, is also known to interact with Kaposi's sarcoma-associated herpesvirus (KSHV) *in vitro*. HMGB1 binds with KSHV latency-associated nuclear antigen (LANA) and stimulates KSHV "replication and transcriptional activator" (RTA) transactivation, thereby facilitating KSHV replication. KSHV may block p53-dependent secretion of HMGB1, thereby increasing intracellular HMGB1 levels even in the setting of senescence. Despite these *in vitro* associations, the role of HMGB1 in KS pathogenesis *in vivo* remains unexplored.

Methods: In a case-control design, cases were HIV-infected adults, sampled throughout Uganda, with biopsy-confirmed KS and no urgent indications for chemotherapy; they were being seen in preparation for the AntiRetrovirals for Kaposi's Sarcoma (ARKS) trial. Controls without KS were derived from the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort, a consecutive sample of HIV-infected adults starting antiretroviral therapy (ART) in Uganda. All biological tests were performed on pre-ART samples. Plasma HMGB1 levels were assayed by an enzyme-linked immunosorbent assay.

Results: We studied 674 subjects: 224 KS cases and 450 non-KS controls (Table). KS cases had a wide spectrum of mucocutaneous KS ranging from oral lesions only to widespread cutaneous dissemination. Non-KS controls had a higher median plasma HMGB1 (7.9; IQR: 5.3 to 12.4 ng/ml) than cases (4.6, IQR: 3.2 to 6.6 ng/ml) ($p<0.001$). Compared to individuals with HMGB1 in the first quartile (i.e., lowest values), there was a 67% (95% CI: 45%-80%), 85% (95% CI: 74%-91%), and 95% (95% CI: 90%-97%) reduction in the odds of KS amongst subjects in the second, third and fourth quartiles of HMGB1, respectively (all $p<0.001$), which was present even after adjusting for age, sex, CD4+ T cell count, plasma HIV RNA, and interleukin (IL)-6 levels (Table).

	Participant characteristics		Multivariable logistic regression for KS	
	KS (n=224)	No KS (n=450)	Odds Ratio (95% CI)	*p* value
Sex				
Men	56%	32%	Ref.	
Women	44%	68%	0.33 (0.22-0.51))	<0.001
Age in years	34 (28-40)*	35 (29-40)*	0.74 (0.57-0.95)†	0.019
CD4+ T cell count/mm^3				
<50	35%	15%	Ref.	
51-100	11%	17%	0.32 (0.16-0.63)	0.001
101-200	23%	39%	0.46 (0.26-0.79)	0.005
201-350	18%	20%	0.77 (0.42-1.42)	0.40
>350	13%	9%	1.65 (0.77-3.52)	0.20
HIV RNA, copies/ml				
≤10, 000	2%	9%	Ref.	
10,001-50,000	9%	19%	2.57 (0.81-8.18)	0.11
50,001-100,000	14%	18%	3.87 (1.23-12.08)	0.02
100,001-500,000	58%	33%	7.89 (2.67-23.33)	<0.001
>500,000	17%	21%	4.06 (1.28-12.85)	0.017
Interleukin-6, pg/ml, by quartile				
Q1 (0.36-1.90)	14%	31%	Ref.	
Q2 (1.91-3.38)	21%	27%	1.57 (0.78-3.17)	0.21
Q3 (3.39-6.54)	32%	22%	4.03 (1.98-8.21)	<0.001
Q4 (6.55-333.69)	33%	21%	2.93 (1.31-6.54)	0.009
HMGB1, ng/ml, by quartile				
Q1 (0.44-4.25)	46%	14%	Ref.	
Q2 (4.26-6.63)	29%	23%	0.33 (0.20-0.55)	<0.001
Q3 (6.64-10.16)	7%	29%	0.15 (0.09-0.26)	<0.001
Q4 (10.7-138.85)	8%	33%	0.05 (0.03-0.10)	<0.001

*median (interquartile range)
†Age, per 10 years

Conclusions: Higher plasma HMGB1 levels are strongly associated with lower occurrence of KS, independent of CD4+ count, plasma HIV RNA and IL-6 levels. This is consistent with the hypothesis that KSHV-mediated intracellular sequestration of HMGB1, reflected by lower extracellular levels, increases KSHV replication and subsequent KS. Alternatively, active HMGB1 secretion by senescent KSHV-infected cells may be a mechanism that suppresses KS development in this setting.

723 The CXCL12/CXCR4-CXCR7 Pathway, a Trio Implicated in Kaposi Sarcoma Pathogenesis

Aude Desnoyer[2]; Francoise Gaudin[2]; Agnes Carlotti[3]; Nicolas Dupin[3]; Francois Boue[2]; Karl Balabanian[2]; **Valérie Martinez-Pourcher**[1]

[1]Hopital Pitié-Salpêtrière, Paris, France; [2]Inserm, Univ Paris-Sud, LABEX LERMIT, UMR_S996, Clamart, France; [3]Dermatology, Paris, France

Background: Lenakap clinical trial (ANRS 154) is a single-arm, multicenter, open label, phase II trial, evaluating the efficacy and safety of lenalidomide in Kaposi's sarcoma (KS) associated with HIV infection (AIDS-KS) despite an effective antiretroviral (ARV) therapy (NCT01282047). KS is a human herpesvirus 8 (HHV-8)-associated disease. It is known that cytokines are required for the development of KS, but so far no biomarker has been identified. We investigated if the CXCL12/CXCR4-CXCR7 pathway, a trio of chemokine and G protein-coupled receptors known to be involved in many cancers, could be a candidate.

Methods: The expression of CXCL12, CXCR4, CXCR7 and different markers, i.e. LANA (HHV-8 latency-associated nuclear antigen), Ki67 (cell proliferation), TUNEL (apoptosis) and VEGF (angiogenesis), were analyzed in AIDS-KS cutaneous biopsies (CBs) (n=16) by immuno-histochemistry. Twenty angiomas and 21 classic KS CBs were used as negative and positive controls respectively. Protein expression was quantified using the Visilog software. Mann-Withney test and Pearson correlation were estimated using Prism 5 software. *P* values <0.05 were considered as statistically significant.

Results: Overall 379 staining of CXCL12, CXCR4, CXCR7, Ki67, LANA, TUNEL and VEGF were performed. Levels of CXCL12, CXCR4 and CXCR7 expression were increased in AIDS-KS and classic KS *versus* angioma CBs ($p<0.0001$), as well as in nodular *versus* macular and papular lesions ($p<0.0005$). Similar results were obtained with Ki67 and VEGF expression ($p<0.0001$). There was no difference in LANA expression in AIDS-KS *versus* classic KS CBs, but LANA was significantly up-regulated in nodular lesions ($p<0.0001$). There were

positive correlations between the trio expression, Ki67, LANA, VEGF and lesion severity (r=0.63-0.81, p<0.0001). The trio expression also correlated with the proliferation rate (r=0.50-0.69, p<0.002), latent HHV-8 level (r=0.56-0.74, p<0.001) and VEGF expression (r=0.41-0.77, p<0.02). No correlation was found with apoptosis level, patient age, $CD4^+$ T cell count, lines of chemotherapy and KS disease duration.

Conclusions: This is the first *in vivo* study that highlights a concomitant up-regulation of the CXCL12/CXCR4-CXCR7 axis in KS. Such deregulation correlates with the disease severity. The CXCL12 signaling axis may be implicated in this virus-related cancer and could serve as a biomarker of KS severity.

THURSDAY, FEBRUARY 26, 2015

Session P-03 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Cancer and Cancer Risk in HIV Subpopulations and Lung Cancer

724 Cancer in HIV-Infected Children: Record Linkage Study in South Africa

Julia Bohlius[6]; Nicky Maxwell[2]; Brian Eley[3]; Hans Prozesky[4]; Shobna Sawry[1]; Karl-Günter Technau[1]; Alan Davidson[2]; Cristina Stefan[5]; **Matthias Egger**[6]
On behalf of IeDEA Southern Africa

[1]University of the Witwatersrand, Johannesburg, South Africa; [2]University of Cape Town, Cape Town, South Africa; [3]Red Cross War Memorial Children's Hospital, Cape Town, South Africa; [4]University of Stellenbosch and Tygerberg Academic Hospital, Cape Town, South Africa; [5]Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa; [6]University of Bern, Bern, Switzerland

Background: The incidence of AIDS- and non AIDS-defining cancers in HIV-infected children and the impact of ART has not been evaluated in sub-Saharan Africa. We examined the incidence of cancer in HIV-infected children enrolled in antiretroviral therapy (ART) programmes in South Africa, using record linkage techniques.

Methods: We linked records of patients aged ≤16 years from five ART programmes (Harriet Shezi and Rahima Moosa in Johannesburg; Khayelitsha, Red Cross and Tygerberg in Cape Town) to the records of the four corresponding paediatric oncology units (Baragwanath and Charlotte Maxeke in Johannesburg; Red Cross and Tygerberg in Cape Town). Records were linked based on folder numbers, names, birth date and sex. Missing CD4 cell counts and percentages were multiply imputed. We calculated incidence rates and hazard ratios (HR) from Cox regression models including ART, sex, age, and immunodeficiency.

Results: Data of 11,707 HIV-infected children (29,348 person-years [pys]) were included in the analysis. Median age at enrolment was 6 years in children developing and 2.5 years in children not developing cancer. We identified 24 incident cancer cases, for an incidence rate of 82/100,000 pys (95% CI 55-122). Kaposi Sarcoma and Non Hodgkin Lymphoma were the most frequent cancers with incidence rates of 34 and 31/100,000 pys, respectively. There were few non AIDS-defining malignancies. In multivariate analysis, children on ART had a lower risk of developing cancer compared to children not on ART. The risk of developing cancer increased with age and more advanced immunodeficiency (Table). In children with cancer, one year survival was 73% (95% CI 61-82%).

Risk of developing cancer among HIV-infected children in South Africa

		Univariable analyses	Multivariable analyses
		HR (95% CI)	HR (95% CI)
ART	Not on ART	1	1
	On ART	0.43 (0.15-1.22)	0.28 (0.09-0.85)
Gender	Male	1	1
	Female	0.74 (0.33-1.67)	0.71 (0.31-1.61)
Age	< 3 years	1	1
	3 to 5	2.99 (0.66 - 13.61)	2.91 (0.64 - 13.25)
	5 to 10	5.38 (1.64 - 17.65)	5.59 (1.71 - 18.35)
	> 10 years	8.30 (2.21 - 31.22)	8.69 (2.30 - 32.80)
Immunodeficiency	None/mild	1	1
	Advanced/severe	1.87 (0.40 - 8.72)	3.69 (1.11 - 12.29)

HR: hazard ratio, ART: antiretroviral therapy; CI: confidence interval

Conclusions: ART reduces the risk of developing cancer in HIV-infected children in South Africa. Early linkage to care and early start of ART may help to further reduce the burden of cancer in these children.

725 High Cancer Risk Among the HIV-Infected Elderly in the United States

Elizabeth L. Yanik; Hormuzd A. Katki; Eric A. Engels
National Cancer Institute (NCI), Rockville, MD, US

Background: HIV-infected people have higher risk of many cancers compared to HIV-uninfected people, but it is unclear if the magnitude of this elevated risk is consistent across age groups. As the proportion of HIV-infected people over age 65 is increasing over time and the elderly population is known to have high cancer risk, it is important to understand the relationship between HIV and cancer in this age group.

Methods: We conducted a case-cohort study that included a 5% sample of Medicare enrollees and all cancer cases ≥65 years of age identified through the Surveillance, Epidemiology, and End Results cancer registries. Non-melanoma skin cancers were not captured. HIV infection was defined through Medicare diagnosis claims. Weighted Cox regression was used to estimate associations between HIV and cancer incidence adjusting for age, race, sex, and calendar year. The absolute risk of cancer over time was calculated accounting for the competing risk of death.

Results: Among 469,954 people in the 5% Medicare sample, 0.08% had an HIV diagnosis. In total, 835,450 cancer cases were identified in cancer registries. Among HIV-infected people, lung and prostate cancers were most common (N=111 each), followed by non-Hodgkin lymphoma (NHL) (N=57). HIV was strongly associated with incidence of Kaposi sarcoma, anal cancer and Hodgkin lymphoma (hazard ratios of 104, 30, and 12, respectively, Table 1). HIV was also associated with incidence of liver cancer, NHL, and lung cancer, but elevations in risk were lower (hazard ratios of 5, 3 and 2, respectively). Among NHL subtypes, HIV was associated with diffuse large B-cell lymphoma and Burkitt lymphoma, but no association was found with other specified NHL subtypes (which comprised 60% of cases in uninfected people). HIV was associated with lower prostate cancer incidence. Over a 1-year period, 2.5% of the HIV-infected elderly were diagnosed with cancer; by 5 years, this proportion increased to 10.2%.

Table 1: Cancer incidence among HIV-infected and HIV-uninfected individuals over the age of 65

	Incidence Rate* (N)		Hazard Ratio (95%CI)	
Cancer Type	**HIV+**	**HIV-**	**Unadjusted**	**Adjusted†**
Kaposi sarcoma	63.5 (12)	0.9 (398)	68.81 (38.14-124.15)	104.49 (56.66-192.69)
Non-Hodgkin lymphoma	304.0 (57)	113.2 (49,918)	2.63 (1.97-3.51)	3.48 (2.59-4.67)
Diffuse large B-cell lymphoma	139.0 (26)	30.1 (13,235)	4.53 (3.02-6.80)	6.24 (4.14-9.41)
Burkitt lymphoma	16.1 (3)	0.7 (304)	22.73 (7.24-71.37)	25.15 (7.99-79.14)
Other Specified	75.0 (14)	68.3 (30,071)	1.07 (0.62-1.83)	1.36 (0.79-2.34)
Unspecified	75.0 (14)	14.4 (6,308)	5.10 (2.97-8.76)	7.61 (4.41-13.12)
Hodgkin lymphoma	42.3 (8)	4.0 (1,752)	10.50 (5.18-21.29)	11.50 (5.65-23.42)
Anus	141.9 (27)	5.0 (2,212)	27.68 (18.56-41.27)	29.96 (19.98-44.92)
Liver	116.5 (22)	22.2 (9,806)	5.15 (3.33-7.98)	4.86 (3.12-7.56)
Lung	582.0 (111)	336.6 (148,217)	1.69 (1.35-2.12)	1.78 (1.42-2.23)
Colorectum	212.6 (40)	230.0 (101,085)	0.91 (0.65-1.27)	1.08 (0.77-1.51)
Breast‡	325.5 (16)	362.1 (94,257)	0.88 (0.51-1.52)	0.96 (0.56-1.65)
Prostate‡	805.1 (111)	854.2 (148,504)	0.92 (0.73-1.17)	0.78 (0.61-0.99)

*Incidence is per 100,000 person-years.
†Hazard ratios are adjusted for sex, race, age at start of follow-up, and calendar year at start of follow-up.
‡Breast cancer incidence was only assessed among women. Prostate cancer incidence was only assessed among men.

Conclusions: HIV infection in the elderly is associated with higher risk for many cancers identified as HIV-associated in younger populations. The relative elevation in NHL incidence is notably lower, but this reflects the high frequency in elderly adults of NHL subtypes less strongly associated with HIV. Given the increased risk associated with both aging and HIV, the elderly HIV-infected population has a sizeable absolute risk of cancer, highlighting the need for cancer prevention and screening efforts in this group.

726 Smoking Outweighs HIV-Related Risk Factors for Non–AIDS-Defining Cancers

Keri N. Althoff[1]; Stephen J. Gange[1]; Chad Achenbach[2]; Lisa P. Jacobson[1]; Angel M. Mayor[3]; Michael J. Silverberg[4]; Amy Justice[5]; Richard Moore[6]; Yuezhou Jing[1]; Kelly Gebo[6]
On behalf of the North American AIDS Cohort Collaboration on Research and Design

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [3]Universidad Central del Caribe, Bayamon, US; [4]Kaiser Permanente Northern California, Oakland, CA, US; [5]Veterans Affairs Connecticut Healthcare System and Yale Schools of Medicine and Public Health, New Haven, CT, US; [6]Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: The increased burden of non-AIDS-defining cancer (NADC) in HIV-infected adults is likely driven by both HIV-related and other cancer risk factors. The objective of this study is to estimate the population attributable fraction (PAF) for smoking and HIV-related risk factors for NADC, interpreted as the proportion of NADC that could be avoided in HIV-infected adults if all participants had the reference group exposure level.

Methods: Adults (≥18 years) participating in one of 16 contributing cohorts to the North American AIDS Cohort Collaboration on Research and Design who were observed for validated NADC diagnosis from January 1, 2000 to December 31, 2009 were included in this analysis. HIV-related risk factors included CD4 count <200 cells/mm^3, HIV RNA ≥200 copies/mL, and clinical AIDS diagnosis. Hepatitis B (HBV) and C (HCV) infections and smoking were also examined. Data on alcohol use, BMI, and HPV infections were not currently available. Risk factors were measured at study entry, with the exception of time-dependent CD4 count and HIV RNA. Cox proportional hazard models with piecewise constant baseline hazard functions were used to estimate adjusted hazard ratios (aHR) and 95% confidence intervals ([,]). The PAFs for the modifiable risk factors of interest were estimated using the methodology described by Laaksonen, *et al*.

Results: Among 39,554 adults who contributed 159,914 person-years, there were 592 incident cancer outcomes distributed as 101 (17%) lung, 96 (16%) anal, 60 (10%) prostate, 54 (9%) Hodgkin, 42 (7%) liver, and 42 (7%) breast cancers. No other cancer type represented more than 5% of the NADC. At baseline, participants who developed NADC were older and had greater proportions with a history of smoking, dyslipidemia, HBV, HCV, and an AIDS diagnosis compared to those without NADC. The PAFs for the variables in the final model can be seen in Figure 1. After excluding lung cancers from the analysis, the PAF for smoking was 39% [23%, 52%].

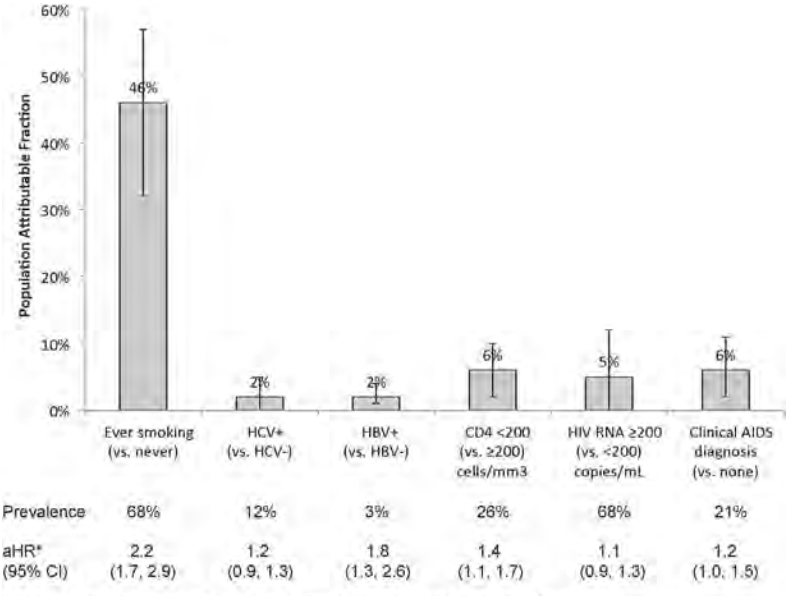


Figure 1: Population attributable fractions and 95% confidence intervals for smoking and HIV-related risk factors for non-AIDS-defining cancers

Conclusions: Programs to prevent smoking initiation among adolescents and young adults at-risk for HIV could prevent up to 46% of NADC in HIV-infected adults. Using ART to preserve immune status, maintain HIV viral suppression, and prevent AIDS-defining illnesses could prevent up to 6% of NADC in HIV-infected adults. In order to reduce the NADC burden in HIV-infected adults, effective interventions to reduce smoking are needed with a continued focus on HIV treatment.

727 High Frequency of Early Lung Cancer Diagnosis With Chest CT in HIV-Infected Smokers

Alain Makinson[1]; Sabrina Eymard-Duvernay[2]; François Raffi[3]; Fabrice Bonnet[4]; Laurence Thirard[5]; Pierre Tattevin[6]; Sophie Abgrall[7]; Jacques Reynes[1]; Vincent Le Moing[1]
on behalf of the ANRS EP48 HIV CHEST Study Team

[1]University Hospital Montpellier, UMI233, Montpellier, France; [2]UMI 233, IRD, University Montpellier 1, Montpellier, France; [3]Nantes University Hospital, Nantes, France; [4]University Hospital Bordeaux, Inserm U897, Bordeaux, France; [5]Tourcoing University Hospital, Tourcoing, France; [6]Pontchaillou University Hospital, Rennes, France; [7]University Hospital Avicennes, Bobigny, France; [8]ANRS, Paris, France

Background: The National Lung Screening Trial has provided compelling evidence of the efficacy of lung cancer screening using chest low-dose computed tomography (LDCT) to reduce lung cancer mortality, but further studies are needed to evaluate LDCT screening in different populations. We sought to study the feasibility and to identify specificities of early lung cancer diagnosis with LDCT in HIV-infected smokers.

Methods: The ANRS EP48 HIV CHEST study is a French, multicentre, prospective study consisting of a one round, millimetric, chest LDCT of HIV-infected subjects ≥ 40 years with a history of cumulative smoking within the last 3 years ≥ 20 pack-years, a CD4 T-lymphocyte nadir cell count < 350/µl, and a last CD4-T cell count > 100 cells/µl. A significant nodule on baseline CT, inducing CT follow up or immediate diagnostic procedures, was defined by a solid or partly solid nodule ≥ 5 mm or a non solid nodule ≥ 8 mm. Follow up and biopsy procedures were suggested in a workup algorithm, with a systematic follow-up of 2 years. Under the hypothesis of a 2.6 increased risk of lung cancer in HIV-infected smokers versus HIV-uninfected counterparts, we estimated lung cancer prevalence to be 3%. Hence, we aimed to enrol 445 patients, and expected 13 diagnosis of lung cancer [95% Confidence Interval, 7-22].

Results: Between March 2011 and June 2012, 442 subjects were enrolled. Median age was 49.8 years, (interquartile range (IQR) 46.3-53.9), 84% were men, median cumulative smoking was 30 pack-years (IQR 25-40), median last CD4 and nadir CD4 cell counts were 574/µl (IQR 408-765) and 168/µl (IQR 75-256) respectively, and 90% had a plasma HIV RNA < 50 copies/ml. A significant nodule was reported in 94 (21%) subjects on baseline CT. Lung cancer (5 staged IA) was diagnosed in 8 subjects (1.81 %), all but one in subjects aged < 55 years (table). There were no serious adverse events due to diagnostic procedures, and 29 subjects were lost to follow up.

Age (yr)	Sex	Lung cancer type	Stage	Smoking (pack-years)	Nadir CD4 count (cells/µl)	Last CD4 value (cells/µl)	Time (wks) between baseline CT and lung cancer diagnosis
45	M	Adenocarcinoma	IA	30	160	637	23
46	F	Adenocarcinoma	IV	52	132	597	76
49	M	Adenocarcinoma	IA	45	321	378	70
50	F	Adenocarcinoma	IV	27	60	590	12
52	M	Adenocarcinoma	IV	35	236	568	66
52	M	Adenocarcinoma	IA	60	214	859	7
54	M	Squamous cell	IA	28	71	345	23
56	M	Adenocarcinoma	IA	34	201	480	7

M : Male; F: Female

Conclusions: Early lung cancer diagnosis and nodule follow up with LDCT are feasible in HIV-infected smokers. Prevalence of lung cancer was within expected range and 5/8 cancers were surgically curable stage IA. The rate of significant nodules on baseline CT was not higher than the ranges published in non HIV-infected screening studies. Lung cancer screening of subjects between the ages of 55-74 years as recommended in the general population may miss substantial numbers of cancers in HIV-infected smokers with a nadir CD4 cell count < 350/µl.

728 CD4 Measures as Predictors of Lung Cancer Risk and Prognosis in HIV Infection

Keith Sigel[1]; Kristina Crothers[2]; Kirsha Gordon[3]; Sheldon Brown[4]; David Rimland[5]; Maria Rodriguez-Barradas[6]; Cynthia Gibert[7]; Matthew B. Goetz[8]; Roger Bedimo[9]; Robert Dubrow[10]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, US; [2]University of Washington School of Medicine, Seattle, WA, US; [3]VA Connecticut Healthcare System and Yale University Schools of Medicine and Public Health, New Haven, CT, US; [4]James J. Peters VA Medical Center, Bronx, NY, US; [5]Atlanta VA Medical Center, Atlanta, GA, US; [6]Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, US; [7]Washington DC Veterans Affairs Medical Center, Washington, DC, US; [8]Los Angeles VA Medical Center, Los Angeles, CA, US; [9]Veterans Affairs North Texas Health Care System, Dallas, TX, US; [10]Yale University School of Public Health, New Haven, CT, US

Background: Immunodeficiency may adversely affect both lung cancer risk and outcomes in the setting of HIV infection. Using data from a large HIV cohort, we investigated relationships between 1) recent and cumulative measures of CD4 and CD8 count and lung cancer incidence and 2) CD4 measures and lung cancer prognosis.

Methods: We followed 26,065 HIV+ subjects from the Veterans Aging Cohort Study (VACS) for a minimum of 2 years, during 1999-2010. We linked VACS with the VA Central Cancer Registry to obtain incident, pathologically confirmed lung cancer cases. Our exposures of interest were longitudinal CD4 (<200 cells/mm^3 [c/mm^3], 200-500 c/mm^3 or >500 c/mm^3), CD4/CD8 (<0.4 or ≥0.4) and CD8 (≥850 c/mm^3 or <850 c/mm^3). We used Cox regression models to investigate the effect of time-updated CD4, CD4/CD8 ratio and CD8 measures on lung cancer risk, including values lagged 12 months, and 12- and 24-month simple moving averages. Models were adjusted for age, sex, race/ethnicity, smoking, and history of pneumonia and COPD. We then collected all non-small cell lung cancer cases from the full VACS (HIV+ and HIV- subjects from 1996-2010) and used conditional probability function regression (a competing risks method to account for higher risk of non-lung cancer death in HIV+) to compare lung cancer-specific survival in 3 groups: HIV- (n=679), HIV+ with CD4≥200 c/mm^3 at cancer diagnosis (n=299) and HIV+ with CD4<200 c/mm3 at cancer diagnosis (n=113). These analyses were adjusted for demographics, comorbidity score, cancer stage and histology, cancer diagnosis year, and cancer treatment.

Results: We identified 325 (1.2%) cases of incident lung cancer in our cohort. In adjusted models (Table 1), a 12 month lagged CD4 count <200 c/mm^3 as well as moving averages of both CD4<200 c/mm^3 and CD4 200-500 c/mm^3 were significantly associated with increased lung cancer incidence. In similar adjusted models, 12-month moving averages of CD4/CD8 ratio <0.4 were also significantly associated with increased risk of lung cancer. Among lung cancer cases, lung cancer-specific survival did not differ between either of the HIV+ groups and the HIV- group (p>0.05) after adjustment.

Table 1. Adjusted hazard ratios for lung cancer by CD4, CD4/CD8 ratio, and CD8 exposures.

Analyses	Lung Cancer Incidence	
	Hazard Ratio*	95% CI
CD4 Analyses		
12 Month Lagged Value		
<200 cells/mm^3	1.6	1.2-2.2
200-500 cells/mm^3	1.2	0.9-1.5
>500 cells/mm^3	Ref	Ref
12-Month Moving Average		
<200 cells/mm^3	2.0	1.4-2.7
200-500 cells/mm^3	1.4	1.1-1.8
>500 cells/mm^3	Ref	Ref
24-Month Moving Average		
<200 cells/mm^3	1.7	1.2-2.4
200-500 cells/mm^3	1.3	1.1-1.7
>500 cells/mm^3	Ref	Ref
CD4/CD8 Ratio Analyses		
12 Month Lagged Value		
<0.4	1.3	0.99-1.7
≥0.4	Ref	Ref
12-Month Moving Average		
<0.4	1.7	1.3-2.1
≥0.4	Ref	Ref
24-Month Moving Average		
<0.4	1.2	0.9-1.5
≥0.4	Ref	Ref
CD8 Analyses		
12 Month Lagged Value		
<850 cells/mm^3	0.9	0.7-1.2
≥850 cells/mm^3	Ref	Ref
12-Month Moving Average		
<850 cells/mm^3	1.0	0.8-1.3
≥850 cells/mm^3	Ref	Ref
24-Month Moving Average		
<850 cells/mm^3	1.0	0.8-1.3
≥850 cells/mm^3	Ref	Ref

*Individual time-updated Cox regression models for risk of lung cancer adjusted for age, sex, race/ethnicity, smoking status, history of pneumonia, and history of COPD

Table 1. Adjusted hazard ratios for lung cancer by CD4, CD4/CD8 ratio, and CD8 exposures.

Conclusions: In our large HIV cohort, we found that several measures of recent and cumulative exposure to immunodeficiency were associated with increased lung cancer risk. CD4 count at time of cancer diagnosis was not associated with cancer-specific survival after accounting for competing risk of non-lung cancer death.

TUESDAY, FEBRUARY 24, 2015

Session P-P1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Cardiovascular Disease Outcomes

729 Cardiovascular Disease Mortality Among HIV-Infected Persons, New York City, 2001–2012

David B. Hanna[1]; Chitra Ramaswamy[2]; Robert C. Kaplan[1]; Regina Zimmerman[2]; Sarah L. Braunstein[2]

[1]Albert Einstein College of Medicine, Bronx, NY, US; [2]New York City Department of Health and Mental Hygiene, Long Island City, NY, US

Background: Cardiovascular disease (CVD) has become more prominent among HIV-infected individuals owing to improved survival, traditional CVD risk factors, and potential effects of antiretroviral therapy (ART). The extent to which CVD mortality rates are changing is unclear but has continued relevance in the context of current ART guidelines.

Methods: The population comprised all persons age 13+ with HIV infection between 2001 and 2012 reported to the New York City HIV Surveillance Registry. Surveillance data were linked with the city Vital Statistics Registry and National Death Index. We examined age-specific and standardized rates of mortality due to major cardiovascular diseases, ICD-10 codes I00-I78. Using log-linear models, we determined time trends in mortality rates among HIV-infected New Yorkers, and compared them with trends among HIV-uninfected New Yorkers derived from Vital Statistics and Census data. Analyses by HIV RNA level began in 2006, the first complete year of comprehensive viral load reporting in New York.

Results: There were 145,009 HIV-infected individuals (1,226,883 person-years) analyzed. Between 2001 and 2012, 29,326 deaths occurred, with annual declines due primarily to fewer HIV-related deaths. Ten percent of deaths were attributed to major cardiovascular diseases, including chronic ischemic heart disease (42% of CVD deaths), hypertensive diseases (27%), and cerebrovascular diseases (10%). While the proportion of deaths due to CVD among HIV-infected individuals increased during the period (6% to 14%, $p<0.001$), the CVD mortality rate among HIV-infected individuals decreased, from 5.4/1000 person-years (95% CI 3.5-7.3) to 2.3 (95% CI 2.0-2.7). After controlling for sex, race/ethnicity, borough of residence, and year, HIV-infected individuals had a significantly higher CVD mortality rate than uninfected individuals in all age groups through age 65, after which CVD mortality was similar or higher in uninfected individuals. CVD mortality was lower among HIV-infected individuals whose last HIV RNA level of each year was suppressed (<400 copies/mL) versus unsuppressed (3.9 vs. 7.7/1000, $p<0.001$).

Conclusions: While CVD mortality rates decreased over the decade, both viremic and virologically suppressed HIV-infected individuals had higher CVD mortality rates than uninfected individuals until age 65. HIV care providers should continue to emphasize preventive measures such as smoking cessation, blood pressure control, and lipid management to reduce CVD risk.

730 Angiographic Restenosis After PTCA in HIV-Infected Patients: Incidence and Predictors

Dominik Promny[3]; **Christoph D. Spinner**[1]; Salvatore Cassese[2]; Isabell Bernlochner[3]; Christian Bradaric[3]; Karl-Ludwig Laugwitz[3]; Adnan Kastrati[2]; Simon Schneider[3]

[1]University Hospital Klinikum Rechts der Isar, Munich, Germany; [2]Deutsches Herzzentrum Muenchen, Munich, Germany; [3]University Hospital Klinikum Rechts der Isar, Munich, Germany

Background: Patients infected with human immunodeficiency virus (HIV) are at risk of accelerated coronary arteriopathy. With the success of combinded antiretroviral therapy, HIV infection has become a chronic condition and percutaneous coronary intervention (PCI) in HIV-infected patients has become an important treatment option. However, dedicated angiographic follow-up studies examining anti-restenotic efficacy in PCI-treated HIV-infected patients are lacking.

Methods: Patients with HIV infection who underwent coronary stenting at our center were enrolled in a dedicated registry. Clinical and laboratory data were prospectively collected in an online database. Angiographic follow-up was scheduled at 6-8 months and predictors of restenosis were evaluated. To investigate individualls with multiple interventions in different segments, generalized estimating equation (GEE) models were employed to consider for repeated measurements (lesions) per subject within the analysis of group differences.

Results: A total of 47 HIV-infected patients were treated for de-novo lesions and prospectively enrolled. Angiographic follow-up was available in 41 patients (87%) with 131 lesions. Overall 103 (78%) lesions were treated with drug eluting stents (DES), 14 (11%) lesions with bare metal stents (BMS) and 14 (11%) lesions with percutaneus coronary intervention (PTCA) balloon alone. Intraprocedural success rate was 100%. The total rate of binary angiographic restenosis was 24% with DES: 19% (p 0.032).

We observed an independent association of binary angiographic restenosis with an elevated CD-8 T cell count (p=0.001), a reduced CD4/CD8 ratio (p=0.036) or an elevated viral load (p=0.001). In GEE analysis, commonly known predictors for restenosis like diabetes or small vessel size are not associated.

Conclusions: The rate of angiographic in-stent restenosis in HIV-infected patients is considerably elevated. CD8 and CD4/CD8-ratio as HIV-specific inflammatory markers are independent predictors of elevated coronary restenosis, while in GEE analysis, commonly known predictors for restenosis like diabetes or small vessel size are not associated.

WEDNESDAY, FEBRUARY 25, 2015

Session P-P2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Dyslipidemia: Mediators and Treatment

731 PCSK9 Is Elevated in HIV+ Patients and May Mediate HIV-Associated Dyslipidemia

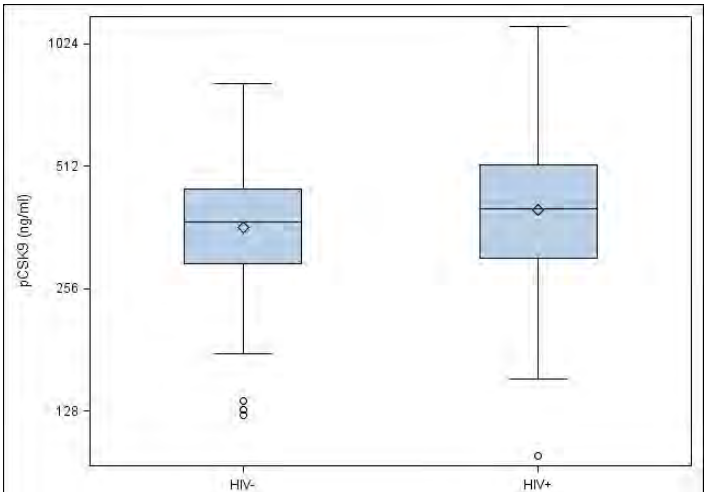
Payal Kohli[1]; Peter Ganz[1]; Yifei Ma[1]; Rebecca Scherzer[1]; Kristinalisa Maka[1]; Scott Wasserman[2]; Rob Scott[2]; Priscilla Hsue[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Amgen, Thousand Oaks, CA, US

Background: Proprotein convertase subtilisin kexin 9 (PCSK9) is induced by inflammation and leads to elevated levels of LDL cholesterol, increasing cardiovascular risk. Increased PCSK9 might explain the dyslipidemia observed in HIV-infected individuals, which has been previously attributed to HIV medication, HIV disease, and/or chronic inflammation. We aimed to compare PCSK9 levels in HIV-infected individuals and uninfected controls and to identify predictors of elevated PCSK9 in HIV disease.

Methods: We measured PCSK9 levels in 567 participants (495 HIV, 72 controls) from an outpatient cohort in San Francisco using a high affinity ELISA assay. Generalized linear models with log link function were used to determine factors associated with PCSK9.

Results: The median age of participants was 50 years (IQR 43-55) and 89% were male, 34% smokers, 25% hypertensive; the median LDL was 103 mg/dL (IQR 80-127), and 21% were on statins. HIV-infected individuals and controls were similar in age, gender, and had similar rates of traditional risk factors except for prior CAD, which was more common among those with HIV (7% vs. 0%). Most (56%) percent of HIV subjects were treated and suppressed on antiretroviral medication with a median HIV duration of 14.5 years, median CD4+ count of 527 (IQR 346-732) cells/mm^3 and nadir CD4+ count of 240 (IQR 96-394) cells/mm^3. Unadjusted PCSK9 levels were 11% higher in HIV subjects vs. controls [mean 430 ng/ml (SD 166) vs. 386 ng/ml (SD134), p=0.015]; in addition, of the patients with extremely elevated PCSK9 levels (>800 ng/ml, n=20), 95% were HIV-infected. After adjustment for demographic factors (age, gender, race) and statin use, HIV remained independently associated with 10% higher PCSK9 levels (p=0.03); results were similar in the treated and suppressed cohort. In addition, older age, other race (comprised of mixed ethnicities, Middle Eastern and Pacific Islanders), statin use, Hepatitis C (HCV), higher triglycerides, current smoking and Lp(a)>90 nmol/L were all independently associated with higher PCSK9 levels in adjusted analysis. In contrast, neither inflammatory markers (IL-6, hs-CRP) nor CD4$^+$ count or HIV viral load were associated with higher PCSK9.



PCSK9 is 10% higher (9% CI 2-22%) (after adjustment for demographics, statin use and cardiovascular risk factors) in HIV-Infected compared with uninfected persons. Note that there are many HIV+ patients having very high PCSK9 levels (>800 ng/mL), suggesting that PCSK9 inhibition may prove to be an attractive target for treating HIV-associated dyslipidemia.

Conclusions: PCSK9 is increased in HIV-infected individuals. Traditional risk factors, HCV, and Lp(a)>90 nmol/L were also independently associated with PCSK9. Future studies should explore whether PCSK9 inhibition may be used to treat dyslipidemia and statin resistance in HIV+ patients.

732 Enhanced, Not Inhibited Monocyte Cholesterol Efflux Characterises Untreated HIV

Jane A. O'Halloran[2]; Therese Herlihy[2]; Alan Macken[2]; Louise Rainford[2]; John S. Lambert[2]; Gerard J. Sheehan[2]; Niall G. Mahon[2]; Leo P. Lawler[2]; Patrick W. Mallon[2]

[1]University College Dublin, Dublin, Ireland; [2]University College Dublin, Dublin, Ireland; [3]University College Dublin, Dublin, Ireland; [4]University College Dublin, Dublin, Ireland; [5]University College Dublin, Dublin, Ireland

Background: Dyslipidaemia in untreated HIV infection is characterised by reduced high density lipoprotein cholesterol (HDL) and increased risk of cardiovascular disease (CVD). In vitro, HIV impairs monocyte cholesterol efflux (MCE) onto apolipoprotein A1 (ApoA1) via the ATP-binding cassette transporter A1 (ABCA1) potentially explaining lower HDL. We aimed to determine if MCE was inhibited in untreated HIV in vivo.

Methods: Using a novel, dynamic ex vivo assay, we compared MCE in HIV positive (HIVpos) subjects not on antiretroviral therapy (ART) and HIV negative (HIVneg) controls matched for age, gender, race, smoking and hepatitis C status. Monocytes were isolated from fasting blood and monocyte intracellular cholesterol (MIC) was measured by florescence and corrected for total cell count before and after cholesterol loading (T=0, 2, 4, 6, 24 hours post loading). MCE was calculated as a ratio of extracellular (supernatant) cholesterol to MIC (EC_T: MIC_T) with an additional 24 hr measure in the presence of ApoA1 (EC_{apoA1}: MIC_{apoA1}). Changes in MCE were correlated with lipids and carotid intima-media thickness (C-IMT). Data are median [IQR]. Comparisons were made using non-parametric analyses.

Results: We recruited 50 HIVpos subjects (52% homosexual, 36% heterosexual; CD4+ 410[268, 588] cells/mm^3; log HIV RNA 4.01[3.52, 4.78] copies/ml) and 50 matched controls. The HIVpos group had significantly lower total, low density lipoprotein and HDL cholesterol but similar triglycerides and C-IMT (table 1). There was no significant between-group difference in fasting MIC (HIVpos 2.0 [1.6, 2.4] versus HIVneg 1.8 [1.6, 2.4] pg/cell, p=0.53) or post cholesterol loaded MIC (HIVpos 7.1 [5.5, 9.6] versus HIVneg 6.7 [5.1, 9.7], p=0.39). However, MCE was significantly and consistently greater in the HIVpos group over time (table 1). The addition of ApoA1 increased EC_{24}:MIC_{24} in both groups, with no between-group difference observed. Higher HDL correlated with lower EC_T: MIC_T ratio (T_2 r=-0.41, T_4 r=-0.34, T_6 r=-0.28, T_{24} r=-0.29, all p≤0.005). Neither C-IMT nor HIV RNA correlated with MCE.

Table 1. Baseline Characteristics and Monocyte Cholesterol Efflux by HIV status

	HIV negative (n=50)	HIV positive (n=50)	p=		HIV negative (n=50)	HIV positive (n=50)	p=
Age (years)	34.5 (30, 43)	35 (29, 41)	0.99	EC_0: MIC_0	-0.04 (-0.05, -0.03)	-0.04 (-0.05, -0.03)	0.48
Male gender (n, %)	39 (78)	40 (80)	0.81	EC_2: MIC_2	0.02 (-0.01, 0.05)	0.07 (0.02, 0.11)	0.001
Caucasian (n, %)	38 (76)	38 (76)	1.0	EC_4: MIC_4	0.06 (0.01, 0.10)	0.09 (0.04, 0.16)	0.004
Current smoker (n, %)	14 (28)	12 (24)	0.65	EC_6: MIC_6	0.11 (0.06, 0.15)	0.16 (0.10, 0.25)	0.003
Cholesterol (mg/dL)	5.0 (4.6, 5.7)	4.3 (3.5, 4.7)	0.000	EC_{24}: MIC_{24}	0.42 (0.32, 0..56)	0.53 (0.40, 0.69)	0.012
HDL (mg/dL)	1.29 (1.15, 1.52)	0.96 (0.82, 1.21)	0.000	EC_{ApoA1}: MIC_{ApoA1}	1.13 (0.92, 1.35)	1.27 (1.06, 1.50)	0.054
LDL (mg/dL)	3.2 (2.6, 3.8)	2.5 (2.1, 3.0)	0.000	C-IMT (mm)	0.77 (0.70, 0.87)	0.78 (0.69, 0.90)	0.94
Triglycerides (mg/dL)	1.08 (0.78, 1.33)	1.25 (0.87, 1.70)	0.09				
Total: HDL ratio	3.8 (3.3, 4.4)	4.4 (3.6, 5.3)	0.01				

Data are median (IQR) unless stated; HDL, high density lipoprotein; LDL, low density lipoprotein; EC, extracellular cholesterol; MIC, monocyte intracellular cholesterol; C-IMT, carotid intima media thickness; ApoA1, Apolipoprotein A1

Table 1. Baseline Characteristics and Monocyte Cholesterol Efflux by HIV status

Conclusions: These data suggests that untreated HIV is characterised by enhanced rather than decreased MCE, with higher MCE correlating with lower HDL. This unexpected finding may reflect up-regulation of MCE pathways compensating for any potential negative effect of HIV on ABCA1-medicated cholesterol efflux. Further research into the pathways involved, the effects of ART and the impact of these findings on CVD pathogenesis is required.

733 Rosuvastatin vs Protease Inhibitor Switch for Hypercholesterolemia: Randomised Trial

Frederick J. Lee[7]; Polyana Monteiro[3]; David Baker[1]; Mark Bloch[2]; Robert Finlayson[8]; Richard Moore[5]; Norman Roth[6]; Jennifer F. Hoy[4]; Esteban Martinez[3]; Andrew Carr[7]

[1]East Sydney Doctors, Sydney, Australia; [2]Holdsworth House Medical Practice, Sydney, Australia; [3]Hospital Clinic, University of Barcelona, Barcelona, Spain; [4]Monash University/Alfred Hospital, Melbourne, Australia; [5]Northside Clinic, Melbourne, Australia; [6]Prahran Market Clinic, Melbourne, Australia; [7]St. Vincent's Hospital, Sydney, Australia; [8]Taylor Square Private Clinic, Sydney, Australia

Background: Optimal management of hypercholesterolaemia in adults receiving a ritonavir-boosted protease inhibitor (rPI) is unknown. The two proven options, statin therapy and rPI switching to a lipid-neutral alternative, have not been compared since the advent of current-generation statins and PIs, despite multiple studies (mostly industry-sponsored) focussed upon rPI switching.

Methods: Adults on rPI-based therapy with plasma viral load <50 cp/mL for ≥6 months, total cholesterol ≥5.5 mmol/L (213 mg/dL) and elevated cardiovascular risk (Framingham score ≥8% at 10 years or family history of premature cardiac disease), and not on lipid-lowering therapy, were randomised to open-label rosuvastatin 10 mg/day or to switch rPI, stratified by cholesterol (> or ≤ 7.0 mmol/L [272 mg/dL]) and rPI type (atazanavir or other); all subjects received standardised diet/lifestyle advice. The primary endpoint was change in fasting total cholesterol at Week 12 (ITT analysis, Wilcoxon rank-sum test); we hypothesized that rosuvastatin would be more effective. Final analyses are reported.

Results: Baseline characteristics (mean [SD] or n [%]) of the 43 subjects were: age 55 (8.5) years; n=42 (98%) male; n=41 (95%) white race; total cholesterol 6.2 mmol/L (240 mg/dL). Baseline rPI types were lopinavir (n=22; 51%), atazanavir (n=12; 28%) and darunavir (n=9; 21%). Within the switch group, the most common rPI substitutes were raltegravir (n=10; 50%) and rilpivirine (n=6; 30%). All subjects adhered to strategy through Week 12. By Week 4, rosuvastatin resulted in greater declines in total cholesterol (24.1% vs. 7.3%, p<0.001), LDL cholesterol, and total:HDL cholesterol ratio, than rPI switch. These changes were maintained at Week 12 (**Table**), with trends to greater declines in cardiovascular risk scores, despite similar weight changes. Conversely, rPI switch caused greater falls in VLDL cholesterol and triglycerides, but more study drug-related adverse events (11 vs. 1, p=0.001 [χ^2]; mostly grade 1 nausea or diarrhoea). HIV viral load rose to 360 cp/mL in 1 rosuvastatin subject by Week 12, but was <50 cp/mL 3 months later without therapy change. One serious adverse event occurred in each arm, both unrelated to study drug/switch. No grade 3-4 laboratory adverse event was seen. No adverse event led to discontinuation of rosuvastatin or switch drug.

Table. Percent changes in primary and secondary endpoints at Week 12

Endpoint	Baseline mean (SD) *All subjects n=43*	Change at Week 12 mean (SD) *rPI Switch n=20*	*Rosuvastatin n=23*	Difference (95% CI)	*p*
Fasting lipids					
Total	6.2 mmol/L (1.2)	-8.7% (10.8)	-21.4% (19.2)	12.7% (2.9, 22.5)	0.003
LDL	4.0 mmol/L (0.9)	-1.0% (20.0)	-29.9% (27.3)	28.9% (14.0, 43.8)	<0.001
VLDL	1.1 mmol/L (1.1)	-37.0% (25.3)	-15.0% (26.6)	22.1% (6.0, 38.1)	0.006
HDL	1.2 mmol/L (0.3)	+0.3% (15.0)	+2.4% (12.1)	2.2% (-10.5, 6.2)	0.574
Total:HDL ratio	5.3 (1.4)	-7.6% (14.1)	-22.7% (18.3)	15.1% (5.0, 25.3)	0.002
Triglycerides	2.2 mmol/L (1.3)	-34.1% (28.0)	-9.8% (31.7)	24.3% (5.7, 42.8)	0.005
Framingham score (10 years)	13.7% (5.1)	-2.1% (2.7)	-3.5% (5.9)	1.4% (-1.4, 4.3)	0.080
D:A:D score (5 years)	8.4% (4.6)	-0.5% (3.1)	-1.6% (3.2)	1.1% (-0.9, 3.1)	0.098
Study drug-related adverse event	..	11 (55%)	1 (4%)	10 (51%)	0.001

CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; VLDL, very low-density lipoprotein.

Conclusions: In adults receiving an rPI, rosuvastatin 10 mg/day for 12 weeks yielded larger decreases in total and LDL cholesterol than rPI switching, and was better tolerated.

734 Application of New ACC/AHA Cholesterol Guidelines to an HIV Clinical Care Cohort

Mosepele Mosepele[4]; Susan Regan[1]; James B. Meigs[1]; Steven Grinspoon[1]; Virginia A. Triant[1]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [4]Harvard School of Public Health, Boston, MA, US

Background: New cholesterol guidelines were issued by the American College of Cardiology (ACC)/ American Heart Association (AHA) in 2013. The impact of the new guidelines on HIV-infected patients is unknown. Our objective was to compare recommendations for statin use under the new guidelines with the established Adult Treatment Panel III (ATPIII) cholesterol guidelines in a large cohort of HIV-infected patients.

Methods: Using the Partners HealthCare System HIV longitudinal cohort, we determined patients' eligibility for statin therapy under the ACC/AHA and ATPIII guidelines as of 2008. We followed them through 2013 to observe actual statin prescription rates, indication for statin recommendations, and cardiovascular disease (CVD) event rates (CHD for ATPIII and atherosclerotic CVD for ACC/AHA) by statin recommendation status (ACC/AHA only, ATPIII only, both, or neither).

Results: In a clinical care cohort of 2239 HIV-infected patients over age 18, 936 (41.8%) patients were recommended for statin therapy by the ACC/AHA guidelines compared with 575 (25.7%) by the ATPIII guidelines. Actual statin prescription rates for patients meeting guidelines for statin therapy were 47% for ACC/AHA and 65% for ATPIII. Of the 405 (18%) patients with discordant statin recommendations, 95% were recommended to be on statin therapy by ACC/AHA and not ATPIII. The most common indication for statin use under the ACC/AHA guidelines was CVD risk ≥7.5% by the new ACC/AHA risk prediction algorithm, and this was the only indication for 46% of patients recommended for statin therapy. Among the group of patients with a CVD outcome event, statin therapy was recommended for 44% of patients by ATPIII and 62% by ACC/AHA. When only one guideline recommended statin therapy for the group of patients with CVD events, the vast majority of cases (39/40) would have qualified for statin therapy by ACC/AHA but not by ATPIII.

Conclusions: In an HIV clinical care cohort, the new ACC/AHA cholesterol guidelines recommend that a higher proportion of patients be on statin therapy and identify an increased proportion of patients with CVD outcome events compared with ATPIII. Despite this increase, nearly 40 percent of patients with a CVD event would not have qualified for statin therapy by the ACC/AHA guidelines. This gap may reflect the novel mechanism of HIV-associated CVD which is not accounted for in general-population guidelines and underscores the need for HIV-specific primary CVD prevention trials.

WEDNESDAY, FEBRUARY 25, 2015

Session P-P3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

ART: Cardiovascular Risk and Hypertension

735 ICAM-1 Overexpression Induced by Abacavir is Mediated by $P2X_7$ Receptors

Carmen de Pablo; Victor Collado-Diaz; Samuel Orden; Cesar Rios-Navarro; Juan Esplugues; **Angeles Alvarez**

University of Valencia, Valencia, Spain

Background: The use of abacavir has been associated with cardiovascular disease. In earlier studies, we have demonstrated that abacavir induces an increase in endothelial ICAM-1 expression and promotes leukocyte recruitment through Mac-1/ICAM-1 interaction. Given the chemical structure of abacavir, we have previously explored the link between abacavir and its proinflammatory effects by interfering in the purine signalling pathway, and have seen that ATP and its $P2X_7$ receptors are involved in the leukocyte accumulation induced by abacavir. The aim of the present study was to evaluate the role of ATP and its receptors in the endothelial ICAM-1 overexpression induced by abacavir.

Methods: Human umbilical vein or arterial endothelial cells (HUVEC or HUAEC, respectively) were pre-treated with antagonists of $P2X_7$ ATP receptors [oxATP (600 μmol/L, 30 min) or A804598 (1 μmol/L, 30 min)] prior to administration of abacavir (10 μmol/L, 24h). Subsequently, ICAM-1 expression was measured by flow cytometry. Data represent the

percentage of median fluorescence intensity vs. control group (100%) and are expressed as media±SEM. Statistical analysis was performed with one-way ANOVA and a Newman-Keuls post-hoc test, with significance *p<0.05 (vs. control) and $^{+}$p<0.05 (vs. abacavir), n≥4.

Results: Clinical concentrations of abacavir (10 μmol/L, 24h) produced an increase in ICAM-1 expression on HUVEC (abacavir 10 μmol/L: 189.8±18.3** vs. 100% control) and HUAEC (abacavir 10 μmol/L: 156.3±6.1** vs. 100% control). When cells were pre-treated with $P2X_7$ receptor antagonists, this ICAM-1 overexpression was reverted on HUVEC [(oxATP 600 μmol/L: 121.9±20.8^{+} vs. 100% control) or (A804598 1 μmol/L: 122.7±10.4^{++} vs. 100% control)] or HUAEC [(oxATP 600 μmol/L: 104.1±7.2^{++} vs. 100% control) or (A804598 1 μmol/L: 113.8±3.9^{++} vs. 100% control)].

Conclusions: Our results suggest that the increased levels of ATP induced by abacavir and its interaction with its $P2X_7$ receptors promote overexpression of ICAM-1 in the venular and arterial endothelium. This process may be responsible for the leukocyte recruitment observed in the vascular damage associated with atherosclerosis and myocardial infarction in HIV patients treated with abacavir.

736 Changes in Platelet Function Following Abacavir Administration: A Pilot Study

Janine M. Trevillyan[2]; Elizabeth E. Gardiner[2]; Jane F. Arthur[2]; Jing Jing[2]; Robert K. Andrews[2]; Jennifer F. Hoy[2]

[1]Monash University, Melbourne, Australia; [2]Monash University, Melbourne, Australia

Background: Abacavir has been linked with cardiovascular disease but the mechanism by which this may occur is unknown. Alterations in platelet function may be involved as the active anabolite of abacavir, carbovir triphosphate, affects intra-platelet guanylyl cyclase activity. This pilot study was performed to determine the impact of abacavir on known and novel markers of platelet function.

Methods: An open label trial was performed in 20 HIV positive adult males on a stable non-abacavir containing regimen for more than 6 months with an undetectable HIV viral load. Patients taking antiplatelets, with known platelet disorders or who were at high cardiovascular risk (Framingham risk score >20%) were excluded. Abacavir (600mg once daily) was added to their usual antiretroviral regimen for 15 days. Blood samples were drawn at baseline, day 15 and day 43 (at completion of 28 day washout). Platelet function was assessed using the FACS-based phosphorylated vasodilator stimulated phosphoprotein (p-VASP) assay and through measurement of the expression and shedding of the pro-thrombotic platelet-specific collagen reception, glycoprotein VI (GPVI). Platelet surface GPVI (pGPVI) was assessed using a fluorescent, phycoerythrin (PE)-conjugated anti-GPVI monoclonal antibody (PE-1G5), plasma levels of shed soluble GPVI (sGPVI) by ELISA.

Results: Participants were 90% Caucasian, mean age 42.2 years (range 29-62), median CD4+ T cell count 660 (IQR 576 – 863). 4 (20%) current smokers. Baseline median platelet count: 198 x 10^9/L (IQR 177-224) with no change over the study period. There was a statistically significant decrease in p-VASP index from baseline to day 15 (median at baseline; 79.1 (95%CI 59.7 - 87.4) vs day 15; 32.6 (95%CI -2.15 - 50.8) p=0.01) which returned to baseline following the 28 day washout period (day 43; 76.3 (95% CI43.7 – 86.8, p=0.71). There was no statistically significant change between baseline and day 15 sGPVI (baseline; 72.5 ng/ml (95% CI 58.3 -81.5) vs Day 15; 45.0 ng/ml (95% CI 33.0 – 98.2) p=0.79) or pGPVI (baseline: 8.38 (95%CI 5.3 – 15.7) vs 7.8 (95%CI 5.7 – 9.7) p=0.81). These results were unaffected by baseline ART (9 on NNRTI, 9 Raltegravir, 6 Protease inhibitor).

Conclusions: Abacavir administration was associated with alterations in the platelet cAMP/cGMP inhibitory pathway which were reversed by cessation and an appropriate washout period. These results require confirmation in a larger heterogeneous population and further work to determine the clinical implications.

737 An RCT of Rilpivirine vs Efavirenz on Cardiovascular Risk in Healthy Volunteers

Samir K. Gupta[1]; James E. Slaven[1]; Ziyue Liu[1]

[1]Indiana University School of Medicine, Indianapolis, IN, US; [2]Indiana University, School of Medicine, Indianapolis, IN, US

Background: Efavirenz (EFV) has recently been shown to impair endothelial function assessed as flow-mediated dilation (FMD), a measure which responds quickly to interventions, but whether this impairment represents an NNRTI class effect is unknown. In the first trial of its kind, we sought to compare endothelial function, metabolic, and inflammatory profiles between EFV and rilpivirine (RPV). The study included healthy volunteers to prevent confounding from HIV infection itself and to allow an evaluation of these drugs' safety profiles as potential pre-exposure prophylaxis.

Methods: We performed a prospective, randomized, open-label trial in 40 HIV-uninfected healthy volunteers who were randomized 1:1 to either EFV or RPV. Vascular indices [FMD, nitroglycerin-mediated dilation (NTGMD), hyperemic volume-time integral (VTI), FMD/VTI of the brachial artery]; metabolic parameters (lipid profiles, HOMA-IR); and inflammatory biomarkers (hsCRP, IL-6, and sVCAM-1) were measured before and after 4 weeks of treatment.

Results: Women (63%) and Blacks (38%) were well-represented in the study cohort. Two participants from each study group discontinued prematurely for adverse events [EFV: 1 for rash, 1 for GI abnormalities; RPV: 1 for headache/insomnia, 1 for rash/drowsiness/vivid dreams]. There were no significant differences (all P>0.2) in 4-week mean (SD) changes in FMD between EFV and RPV [0.089 (3.7) vs 0.63 (2.4) %], NTGMD [0.42 (3.4) vs 1.59 (5.7) %], VTI [0.02 (0.3) vs 0.01 (0.3) cm], or FMD/VTI [-0.67 (5.6) vs 0.54 (5.6) %/cm]. There were also no significant differences in 4-week changes in hsCRP, IL-6, sVCAM, HDL-C, or triglycerides. However, EFV led to significant increases in total cholesterol [19.39 (23.9) vs -5.78 (16.5) mg/dL; P<0.001] and LDL-C [13.29 (19.5) vs -2.24 (13.4) mg/dL; P=0.009] and to non-significant decreases in HOMA-IR [-0.43 (1.5) vs 0.60 (1.6); P=0.056] compared to RPV. Both agents were generally well-tolerated without differences in adverse events.

Conclusions: We did not detect any differential effects between RPV and EFV on endothelial function, other physiologic vascular indices, inflammatory biomarkers, or safety parameters over 4 weeks in healthy volunteers. However, EFV was associated with significantly greater increases in total cholesterol and LDL-C compared to RPV. These results suggest RPV has an inherently benign cardiovascular safety profile and may be a safe agent to use for PrEP, although longer-term studies are required for confirmation.

738 Elvitegravir Reduces Monocyte Activation and Vascular Inflammation More Than Efavirenz

Corrilynn O. Hileman[1]; Bruce Kinley[1]; Valeska Scharen-Guivel[2]; Kathy Melbourne[2]; Javier Szwarcberg[2]; Janet Robinson[1]; Michael M Lederman[1]; Grace A. McComsey[1]

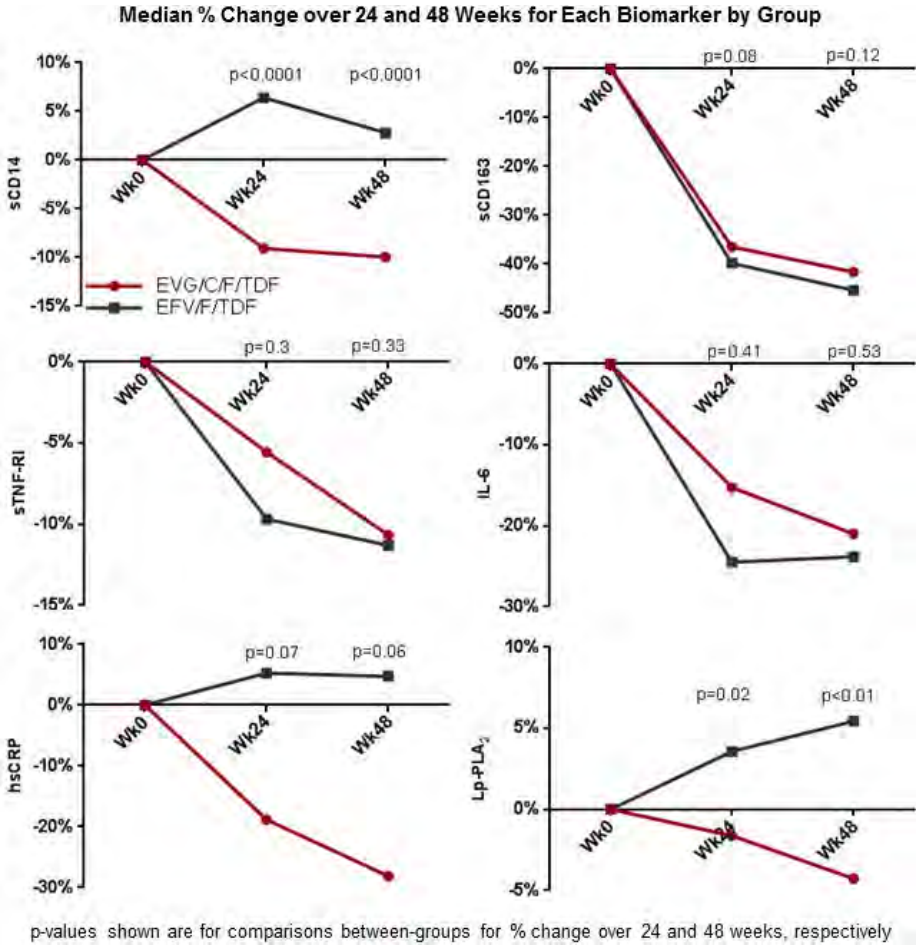
[1]Case Western Reserve University, Cleveland, OH, US; [2]Gilead Sciences, Inc., Foster City, CA, US

Background: Heightened inflammation and monocyte activation may drive cardiovascular disease and other comorbidities in HIV. Little is known about the differential effects of antiretrovirals on immune activation.

Methods: A randomized, double blind trial in ART-naïve HIV-infected adults comparing safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir (EVG/C/F/TDF) and efavirenz/emtricitabine/tenofovir (EFV/F/TDF) was previously performed. From a random sample of participants who achieved HIV-1 RNA of <50 copies/mL at week 48, we conducted a comparison of changes from baseline to week 24 and 48 in biomarkers of monocyte activation (sCD14 and sCD163), systemic (sTNF-RI, IL-6 and hsCRP) and vascular inflammation (Lp-PLA_2). Multivariable linear regression was used to determine predictors of change in sCD14 and Lp-PLA_2.

Results: 200 participants were included (100 per group). Baseline demographics and clinical indices were balanced and comparable to the overall population (n=700). Overall, 89% were men, 65% Caucasian, with median age 38 years, CD4 count 372 cells/mm^3 and HIV-1 RNA 64,900 copies/mL. At baseline, biomarkers were similar between groups. Significant differences favoring EVG/C/F/TDF were noted for changes in sCD14 and Lp-PLA_2 and neared significance for hsCRP (see Figure). Weight, lipid and CD4 changes were similar between groups. The 48 week changes in sCD14 and Lp-PLA_2 remained significantly different between groups after adjustment for changes in all clinically important

variables (p<0.001). Independent predictors of change in sCD14 were randomization group, baseline sCD14, CD4 and HDL-cholesterol, and changes in weight, eGFR, hsCRP and sCD163; and for Lp-PLA$_2$ were baseline Lp-PLA$_2$, LDL-cholesterol and IL-6, and changes in cholesterol, triglycerides, sCD14 and sCD163.



Conclusions: Initiation of ART with EVG/C/F/TDF led to greater decreases in sCD14 and Lp-PLA$_2$ when compared with EFV/F/TDF. Randomization group independently predicted changes in sCD14, and changes in monocyte activation independently predicted changes in Lp-PLA$_2$. There appears to be a different effect of the integrase inhibitor EVG compared to EFV on HIV-related immune activation which may in turn impact vascular inflammation.

739 Impact of Antiretroviral Drugs on Hypertension in HIV-Positive Persons: D:A:D Study

Camilla I. Hatleberg[1]; Lene Ryom[1]; Antonella d'Arminio Monforte[2]; Eric Fontas[3]; Peter Reiss[4]; Ole Kirk[1]; Wafaa M. El-Sadr[5]; Stéphane De Wit[6]; Jens D. Lundgren[1]; Caroline Sabin[7]
On behalf of the D:A:D Study group

[1]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [2]San Paolo University Hospital, Milan, Italy; [3]Nice University Hospital, Nice, France; [4]Academic Medical Center, University of Amsterdam, Amstredam, Netherlands; [5]Columbia University, New York, NY, US; [6]Centre Hospitalier Universitaire St. Pierre Hospital, Brussels, Belgium; [7]University College London, London, United Kingdom

Background: Previous studies have documented that hypertension in HIV-positive (HIV+) individuals is associated with traditional risk factors such as older age, male gender, diabetes, dyslipidemia and high body mass index (BMI). However, controversy remains as to whether the exposure to antiretroviral therapy (ART) poses additional risk. We investigated this issue in the D:A:D Study.

Methods: The incidence of hypertension (systolic blood pressure (BP) ≥140 and/or diastolic BP ≥90 mmHg and/or initiation of antihypertensive treatment) in patients with normal BP at baseline was determined overall and in various strata defined by demographic, metabolic- and HIV-related factors, including cumulative exposure (/year) to each ART drug. Predictors of hypertension were identified using uni- and multivariable Poisson regression models, adjusted for potential confounders. Follow-up was from 1/2/99 until the earliest of confirmed hypertension, 6 months after last visit or 1/2/2013.

Results: Of 33,278 included persons, 7636 (22.9%) developed hypertension over 223,149 person years (PYRS) (rate ratio (RR): 3.42 [95% CI 3.35-3.50]/100 PYRS). The demographic and HIV-related factors independently associated with a significantly increased rate of hypertension in multivariable models were male gender (RR 1.39 [1.30-1.48]), older age (vs. <30 years): 30-39 years (1.58 [1.37-1.82]); 40-49 years (2.60 [2.27-2.99]); 50-59 years (4.15 [3.60-4.78]); ≥60 years (6.09 [5.24-7.08]), black African origin (1.39 [1.25-1.54]), mode of HIV acquisition via injection drug use (1.09 [1.01-1.18]) and previous AIDS diagnosis (1.15 [1.09-1.20]). In univariate analyses, there were significant associations between cumulative exposure to almost all ART drugs and risk of hypertension. However, after adjustment for demographic, HIV-related factors and smoking, only abacavir, nevirapine, ritonavir and indinavir continued to be significantly associated with an increased risk of hypertension, although effects were small (Table). The estimates were similar when additionally adjusting for metabolic factors potentially on the causal pathway (Table).

Table: Association between cumulative exposure to each ART drug (/year) and incident hypertension: Results from fully adjusted Poisson regression models*

	Adjusted for demographic, HIV-related factors and smoking[1]		Additionally adjusted for factors potentially on the causal pathway[2]	
	RR [95% CI] /year	p-value	RR [95% CI] /year	p-value
Exposure to:				
Lamivudine	1.01 [1.00-1.01]	0.15	1.01 [1.00-1.01]	0.21
Abacavir	1.01 [1.00-1.02]	0.05	1.01 [1.00-1.02]	0.25
Tenofovir	1.01 [0.99-1.02]	0.39	1.00 [0.99-1.02]	0.71
Emtricitabine	0.97 [0.95-1.00]	0.04	0.98 [0.96-1.01]	0.14
Efavirenz	0.99 [0.98-1.01]	0.29	0.99 [0.97-1.00]	0.02
Nevirapine	1.02 [1.01-1.03]	0.0001	1.02 [1.00-1.03]	0.006
Lopinavir	0.99 [0.97-1.01]	0.18	0.99 [0.97-1.00]	0.14
Ritonavir	1.02 [1.00-1.03]	0.02	1.01 [0.99-1.02]	0.26
Atazanavir	0.98 [0.96-1.00]	0.12	0.97 [0.95-0.99]	0.004
Indinavir	1.03 [1.02-1.05]	0.0001	1.02 [1.01-1.04]	0.002
Nelfinavir	1.00 [0.99-1.02]	0.64	1.00 [0.98-1.01]	0.85
Darunavir	0.94 [0.88-0.99]	0.02	0.92 [0.87-0.97]	0.004

[1]Adjusted for gender, participating cohort, ethnic group, mode of HIV acquisition (time-fixed), calendar year, age, smoking status and previous AIDS diagnosis (time-updated);
[2]Additionally adjusted for total cholesterol, triglycerides, use of lipid-lowering drugs, lipodystrophy, BMI, diabetes and eGFR (all time-updated).

Conclusions: We did not find evidence for any strong independent association between exposure to any of the ART drugs and the risk of hypertension. Established risk factors for hypertension in the general population were confirmed in this population of HIV+ persons, providing reassurance that screening policies for hypertension in HIV+ persons should follow algorithms used for the general population.

740 Population-Based Assessment of Hypertension Among HIV Patients in Rural Uganda

Dalsone Kwarisiima[1]; Prashant Kotwani[3]; Norton Sang[4]; Florence Mwangwa[2]; Vivek Jain[3]; Dathan Byonanebye[2]; James Ayieko[4]; Laura Balzer[5]; Diane Havlir[3]; Moses R. Kamya[6]

[1]Makerere University Joint AIDS Program, Kampala, Uganda; [2]Infectious Disease Research Collaboration, Kampala, Uganda; [3]University of California San Francisco, San Francisco, CA, US; [4]Research Care Training Program, Kenya Medical Research Institute, Nairobi, Kenya; [5]University of Berkeley, Berkeley, CA, US; [6]Makerere University College of Health Sciences, Kampala, Uganda

Background: Following ART scale-up, there is an aging HIV+ population at risk for non-communicable diseases such as hypertension (HTN). We estimated HTN prevalence among adults ≥18 years attending multi-disease health campaigns in 20 rural Ugandan communities in the SEARCH Study (NCT01864603). We investigated (a) HIV as an independent risk factor for HTN, given conflicting prior literature on this topic, and (b) awareness and control of hypertension in HIV+ adults.

Methods: Blood pressure (BP) was measured on 65,274 adults by sphygmomanometry. HTN was defined as SBP≥140 or DBP≥90 on 3 repeat measurements or self-reported current use of anti-hypertensives. We tested for HIV and collected demographics, body mass index (BMI), socio-economic status (SES), education, and alcohol use on all participants. We computed the crude and standardized prevalence of HTN within the population sample as well as estimates normalized to WHO standard population distribution. Logistic regression (adjusting for demographics, BMI, SES, education, alcohol use, region [east vs. west Uganda], viral load and CD4 count) was used to identify independent predictors of HTN among HIV+ persons.

Results: Overall, adult prevalence of HTN was 12.9% (95%CI: 12.6%-13.1%), and was 15.6% normalized to WHO standard population. After multivariate adjustment, significant predictors of HTN included older age, male sex, higher BMI, no education, more alcohol use, region and HIV infection. The adjusted relative odds of HTN were 1.2-times higher among HIV negatives than positives (95%CI: 1.05-1.35). Among HIV+ adults, hypertension prevalence was 10.2% (95%CI: 9.2%-11.2%). Among HIV+, HTN+ adults, 79.1% had no prior HTN diagnosis and 14.5% reported being on HTN treatment. Among HIV+ HTN+ adults on treatment, 53.7% achieved BP control. In multivariate analyses, significant predictors for HTN were older age, higher SES and region. Viral suppression of HIV did not significantly predict HTN.

Conclusions: In this large Ugandan study, we found a substantial prevalence of hypertension in the general population and among HIV positives. The majority was previously undiagnosed. HIV positivity predicted lower odds of HTN after adjustment for common risk factors, consistent with smaller previous African studies. Prospective data with more extensive adjustment for confounding by SES and other factors are needed to understand the reason for this association.

TUESDAY, FEBRUARY 24, 2015

Session P-P4 Poster Session — Poster Hall

2:30 pm – 4:00 pm

What Predicts Risk for CVD in HIV?

741 CD4/CD8 Ratio, Age, and Serious Noninfectious Outcomes in HIV-Infected Adults

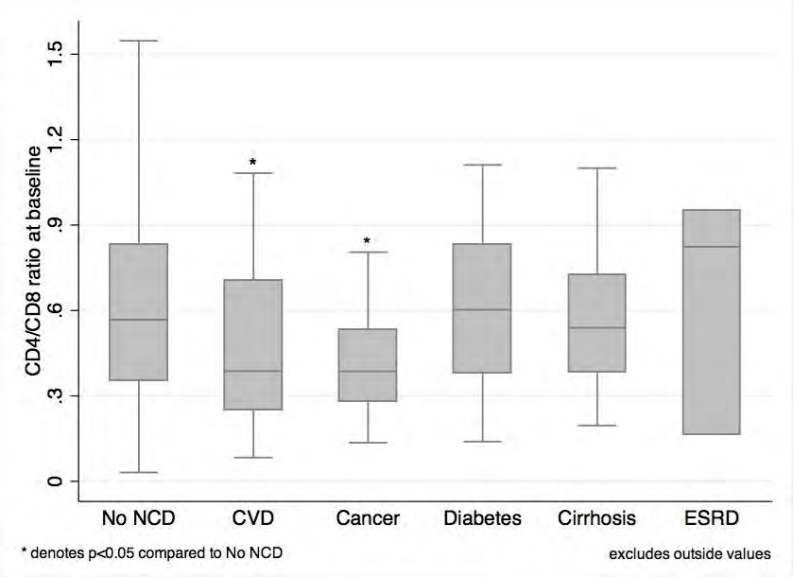
Jessica L. Castilho; Megan Turner; Sally Bebawy; Bryan E. Shepherd; Timothy Sterling

Vanderbilt University School of Medicine, Nashville, TN, US

Background: In virologically suppressed HIV-infected adults, CD4/CD8 ratio has been inversely associated with risk of non-communicable diseases (NCDs). Very low CD4/CD8 ratio (<0.4) despite antiretroviral therapy (ART) also correlates with higher measures of immunosenescence. The interaction of age and CD4/CD8 and its association with future NCD events has not been described.

Methods: We assessed the association of CD4/CD8 ratio and serious NCDs (cardiovascular [coronary artery, cerebrovascular, and peripheral vascular disease], malignancy, liver, and renal diseases) in a cohort of HIV-infected adults after their first year of suppressed HIV RNA (defined as baseline). We examined patient characteristics by baseline CD4/CD8 ratio and CD4/CD8 ratio change from baseline by linear regression. We used Cox proportional hazard models to assess baseline CD4/CD8 ratio and risk of future NCDs.

Results: Between 1998-2010, 1700 patients achieved virologic suppression for one year and were included in this study (median follow-up time=3 years). Compared to those with CD4/CD8 ratio ≥0.7, patients with low CD4/CD8 ratio (<0.4) were older (median 44 vs. 40 years, $p<0.01$), more likely to be male (86 vs. 70%, $p<0.01$), and had lower CD4+ lymphocyte counts (median 279 vs. 640 cells/mL, $p<0.01$). There was no difference in prior ART or follow-up duration. Among those with consistent virologic suppression after three years (n=454), older patients (≥50 years) had lower CD4/CD8 gain compared to younger patients (<40 years), after adjusting for baseline ratio (beta = -0.07, $p=0.03$). There were 123 serious NCDs, including 48 cardiovascular disease (CVD) and 30 cancer events (median time to first CVD or cancer event=2.3 years). Compared to patients with no NCDs during follow-up, only those with CVD and cancer outcomes had statistically lower baseline CD4/CD8 ratios (see Figure). In a model adjusting for age, sex, and CD4+ lymphocyte count, a higher CD4/CD8 ratio remained associated with a lower risk of CVD and cancer events (composite aHR per 0.1 increase = 0.90 [95% CI: 0.81-1.00]). An interaction term for age and CD4/CD8 ratio was not statistically significant ($p=0.46$).



Distribution of CD4/CD8 ratio by non-communicable disease (NCD) outcomes in a cohort of 1,700 virologically suppressed HIV-infected adults, 1998-2010

Conclusions: Low CD4/CD8 ratio after one year of suppressed HIV RNA was independently predictive of serious CVD and cancer events. Older adults had lower CD4/CD8 ratio and had less improvement in CD4/CD8 ratio over time. Further study of CD4/CD8 ratio as a biomarker for immunosenescence and risk factor for CVD and cancer in aging HIV-infected adults is needed.

742 Relationship Between Confirmed eGFR and Cardiovascular Disease in HIV-Positive Persons

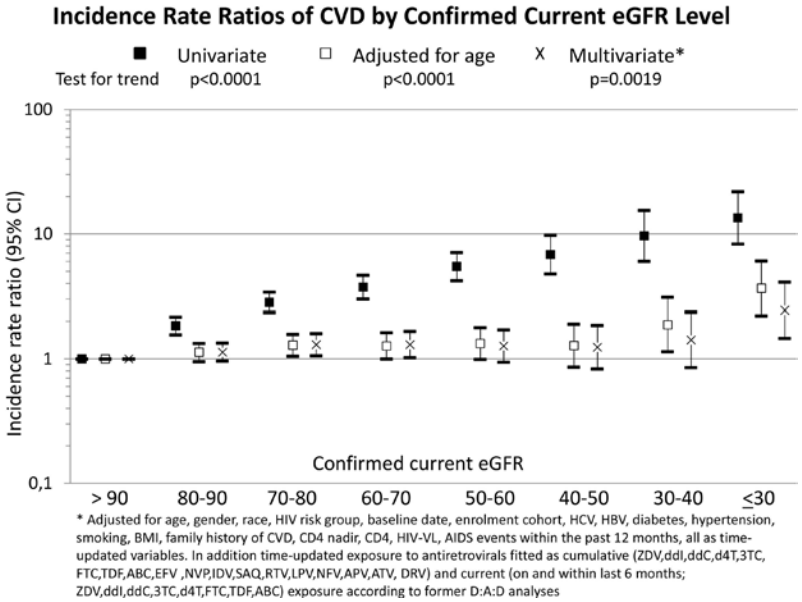
Lene Ryom[1]; Jens D. Lundgren[1]; Peter Reiss[2]; Michael Ross[3]; Christoph Fux[4]; Philippe Morlat[7]; Olivier Moranne[5]; Colette Smith[6]; Caroline Sabin[6]; Amanda Mocroft[6]
On Behalf of the D:A:D Study Group

[1]CHIP, Department of Infectious Diseases and Rheumatology, Rigshospitalet and University of Copenhagen, Copenhagen, Denmark; [2]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; [3]Division of Nephrology, Mount Sinai School of Medicine, New York, New York City, NY, US; [4]Clinic for Infectious Diseases and Hospital Hygiene, Kantonsspital Aarau, Aarau, Switzerland; [5]Nephrology department, Public Health department, CHU Nice, Nice, France; [6]University College London, London, United Kingdom; [7]University of Bordeaux, INSERM U 897, CHU de Bordeaux, Bordeaux, France

Background: While the association between impaired kidney function and cardiovascular disease (CVD) is well established in the general population, this association remains poorly elucidated in HIV-positive individuals. As prior studies in HIV have focused on unconfirmed measures of kidney function, which are subject to random variation and acute illness, the influence of sustained kidney impairment is less clear.

Methods: D:A:D study participants with ≥2 eGFRs (Cockcroft Gault) measured after 1/1/2004 were followed until the earliest of CVD, last visit plus 6 months or 1/2/2013. CVD was defined as centrally validated (fatal and non-fatal) myocardial infarction, stroke, angioplasty, bypass, or carotid endarterectomy. Poisson regression stratified according to confirmed current eGFR level was used to model the incidence rate ratios of CVD, while adjusting for demographics, antiretroviral treatment, traditional HIV, cardiovascular and renal risk factors.

Results: During a median follow-up of 6.3 years (IQR 4.1-7.9) 1,033 of 34,793 included persons developed CVD (incidence 5.1/1000 PYFU [95% CI 4.8-5.4]). Those included were predominantly Caucasian (48%), male (74%), had homosexual HIV transmission (46%), a median age of 41 years (IQR 35-48), CD4 count of 440 cells/mm^3 (IQR 290-623) and a median time between eGFRs of 3.8 months (IQR 2.8-5.7). There was a clear relationship between confirmed eGFR at baseline and incident CVD with 1.7% [95% CI 1.5-1.9] estimated to have progressed to CVD at 5 years among those with eGFR >90 ml/min/1.73m^2, increasing to 23.4% [95% CI 6.9-39.8%] among those with eGFR ≤30 ml/min/1.73m^2. The strong relationship between a low confirmed current eGFR and CVD in unadjusted analyses was primarily explained by increasing age in adjusted analyses, although a strong trend for increased CVD rates with decreasing eGFR levels remained, largely driven by high rates in those with eGFR ≤30 ml/min/1.73m^2 (figure). This finding was consistent in different age groups (p=0.43, test for interaction). Analyses were consistent after accounting for death as a competing risk for CVD.



Conclusions: In a large contemporary cohort of HIV-positive individuals we observed a strong relation between confirmed impaired kidney function and incident CVD. This finding highlights the need for an intensified monitoring for emerging CVD, in particular in older individuals with continuously low eGFR levels, and an increased focus on renal preventive measures.

743 Smoking, Other Substance Use and Coronary Atherosclerosis Among HIV-Infected and Uninfected Men

Sean G. Kelly[1]; Michael Plankey[3]; Wendy Post[2]; Xiuhong Li[2]; Ron Stall[4]; Lisa P. Jacobson[2]; Mallory Witt[5]; Lawrence Kingsley[4]; Christopher Cox[2]; Frank J. Palella[1]

[1]Northwestern University, Chicago, IL, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]Georgetown University, Washington, DC, US; [4]University of Pittsburgh, Pittsburgh, PA, US; [5]University of California Los Angeles, Los Angeles, CA, US

Background: HIV infection is associated with subclinical atherosclerosis. Recreational substance use is prevalent among HIV-infected (HIV+) persons. Associations between substance use and coronary plaque by HIV serostatus are not well-characterized.

Methods: We studied 1005 men who have sex with men in the Multicenter AIDS Cohort Study (612 HIV+ and 384 HIV-uninfected [HIV-]), all of whom had non-contrast CT scanning to measure coronary artery calcium (CAC) and 764 had coronary CT angiograms. Self-reported recreational substance use, including alcohol (ETOH), tobacco, stimulants, marijuana, inhaled nitrites, and drugs to treat erectile dysfunction (EDD) was obtained at each semiannual visit beginning 10 years prior. Logistic (for plaque presence) and linear (for log-transformed plaque scores if >0) regression models were performed stratified by HIV serostatus and adjusted for age, race, education, cardiovascular disease risk factors and, for HIV + men, HIV clinical factors.

Results: In HIV+ men, current smoking was more prevalent than in HIV- men (31% vs. 22%), as were greater pack years (pk-yrs) of smoking (HIV+, 14±19; HIV-, 12±18). In HIV+ men only, current smoking was positively associated with presence of CAC, any plaque, calcified plaque (CP) and coronary artery stenosis >50% (OR 2.3 [1.3-3.9], 2.3 [1.1-4.7], 2.0 [1.1-3.9], 2.6 [1.1-6.0]), former smoking with CP and stenosis (OR 2.2 [1.2-3.8], 2.2 [1.1-4.7]) and heavy ETOH use (>14 drinks/week) with stenosis (OR 4.7 [1.5-14.8]). In HIV- men, cumulative pk-yrs of smoking was associated with CAC (OR 1.02 [1.002-1.03] per year) and stenosis (OR 1.02 [1.0001-1.04]), moderate (1-14 drinks/week) and heavy ETOH use were inversely associated with CAC extent (β -0.69, -1.14; p=0.02, p=0.02), heavy ETOH use inversely with CP extent (β -0.89, p=0.001) and binge drinking (≥ 5 drinks ≥ once in the prior 30 days) positively with CP extent (β 0.85, p=0.02). Marijuana use was positively associated with CAC extent in HIV- men (β 0.005, p=0.02) and EDD use with CP extent in HIV+ men (β 0.06, p=0.02). No significant associations between plaque and cumulative stimulant or nitrite use were seen.

Conclusions: Smoking is common and strongly associated with subclinical coronary atherosclerosis among HIV+ men. Our findings underscore the value of effective smoking cessation strategies targeting HIV+ persons to decrease cardiovascular disease burden. Other forms of substance use, other than ETOH, were not consistently associated with atherosclerosis.

744 Pericardial Fat Density: A Novel Marker of Cardiometabolic Risk in HIV Infection

Chris T. Longenecker; Mark Schlucter; Yiying Liu; Grace A. McComsey

Case Western Reserve University, Cleveland, OH, US

Background: Pericardial fat volume is associated with inflammation, insulin resistance, and vascular disease in HIV-infected patients on antiretroviral therapy (ART). The relationship between pericardial fat density, inflammation, and cardiometabolic risk in this population is unknown.

Methods: Pericardial fat volume and density [mean Hounsfield Units (HU)] were measured by cardiac computed tomography in 147 HIV-infected patients on ART. Pearson correlations were used to examine the relationship between fat density and markers of cardiometabolic risk. Multivariable linear regression was used to explore the relationship of pericardial fat to insulin resistance. Non-normally distributed variables were log-transformed for all analyses.

Results: Median (Q1, Q3) age was 46 (40, 53) years; 78% were male and 68% African American; 49% were on a protease inhibitor. Median homeostatic model of insulin resistance (HOMA-IR) was 1.84 (1.06, 3.33). Median pericardial fat volume was 68 (47, 92) ml and density was -86.8 (-88.7, -85.0) HU. Pericardial fat volume and density were modestly negatively correlated (r= -0.366, p<0.001). Pericardial fat density negatively correlated with duration of ART use (r= -0.206, p=0.017) and protease inhibitor use (r= -0.227, p= 0.014). In contrast to volume, density did not correlate with measures of total body adiposity (BMI r=0.057 and total body fat by DEXA r=-0.034, both p>0.4), but was negatively correlated to waist-hip ratio (-0.337, p<0.001). In a multivariable model, pericardial fat density was associated with insulin resistance independent of pericardial fat volume, BMI, metabolic syndrome, and biomarkers of monocyte immune activation and systemic inflammation (see Table).

.

Multivariable linear regression model of the relationship between pericardial fat density and insulin resistance (logHOMA-IR)

	β	P value
Pericardial fat density (HU)	-0.150	0.024
Pericardial fat volume (ml)*	0.096	0.232
Non-HDL (mg/dL)	0.063	0.296
Metabolic syndrome (yes vs. no)	0.658	<0.0001
BMI (kg/m2)	0.186	0.017
Soluble CD163 (ng/ml)*	0.142	0.019
Soluble CD14 (ng/ml)*	-0.097	0.108
Current Smoker (yes vs. no)	-0.282	0.023

Candidate variables were demographics, traditional cardiovascular risk factors, HIV disease factors, measures of total body and regional adiposity, and biomarkers of systemic inflammation and immune activation. Variables were selected by forward and backward selection, with a significance level of $p<0.15$ for inclusion in the model. Pericardial fat volume was forced into the final model. Parameter estimates are expressed per standard deviation increase for continuous variables or yes vs. no for dichotomous variables. HOMA-IR, Homeostatic model assessment of insulin resistance; HU, Hounsfield Units; HDL, high-density lipoprotein; BMI, body mass index. * = Non-normally distributed variables were log-transformed prior to analyses. Model $R2 = 0.4383$

Conclusions: Pericardial fat density, a simple measure obtained from non-contrast cardiac CT, is a novel marker of insulin resistance that is independent of pericardial fat volume and measures of total body adiposity. Further studies should examine the utility of this measure to characterize adipose tissue dysfunction in patients with chronic HIV infection

745 The Effect of Physical Activity on Cardiometabolic Health and Inflammation in HIV

Sahera Dirajlal-Fargo[1]; Allison R. Webel[2]; Bruce Kinley[3]; Danielle Labbato[3]; Ying Jiang[4]; Sara M. Debanne[4]; Grace A. McComsey[1]

[1]Rainbow Babies and Children's Hospital, Case Western Reserve University School of Medicine, Cleveland, OH, US; [2]Frances Payne Bolton School of Nursing Case Western Reserve University, Cleveland, OH, US; [3]University Hospitals Case Medical Center, Cleveland, OH, US; [4]Case Western Reserve University, Cleveland, OH, US

Background: In HIV-uninfected populations, physical activity decreases mortality and reduces inflammation. Persistent inflammation is a potential cause for increased co-morbidities in HIV+ adults, yet the evidence examining the effect of physical activity on cardiometabolic health and inflammation in this population is limited. This analysis examines the relationship between physical activity and markers of cardiometabolic health and inflammation.

Methods: We conducted a nested study within the SATURN-HIV trial in which 147 HIV+ adults on stable antiretroviral therapy (ART), with HIV-1 RNA< 1,000 copies/mL and LDL-cholesterol <130mg/dL were randomized to 10 mg daily rosuvastatin or placebo. Measures of physical activity, cardiometabolic health, and inflammation were assessed at baseline and 24 weeks later. Spearman correlations were used to explore relationships between physical activity, inflammation and CVD risk markers. Multivariable analyses were conducted to assess associations with physical activity.

Results: Median age (Q1, Q3) was 46 (40.4, 52.7) years, 80% were male, 69% were African American and 46% on protease inhibitors. Baseline median physical activity was 49.5 (30.1, 67.9) minutes per week. Physical activity was significantly correlated with several markers of cardiometabolic health and inflammation (all $p\leq0.05$) (see table). After adjustment for factors known to affect cardiometabolic health and inflammation, physical exercise remained independently associated with markers of vascular disease (carotid bulb intima-media thickness; $\beta=<-0.01$, $p=0.03$) and endothelial function (brachial hyperemic velocity-time integral; $\beta= <0.01$, $p=0.04$). In addition, physical activity ($\beta =0.003$, $p<0.01$) was independently associated with insulin resistance (HOMA-IR), even after adjustment for diabetes risk factors, HIV factors, body composition, and inflammation. After 24 weeks, median physical activity was 46.7 (31.4, 64.8) minutes per week and there was no difference between the statin and placebo groups. Changes in physical activity were correlated with changes in insulin resistance ($\alpha=0.19$, $p=0.03$).

Spearman Correlation Analysis- Any Physical Activity (minutes per Week)		
	α Coefficient	*p*-value
Cystatin C (mg/L)	-0.16	0.05
Soluble TNF-α receptor 1	-0.20	0.04
Carotid bulb intima-media thickness	-0.24	<0.01
Brachial hyperemic velocity-time integral	0.17	0.04
Spearman Correlation Analysis- Vigorous Physical Activity (min/Week)		
Leptin (pg/mL)	-0.20	0.02
HOMA-IR	-0.33	<0.01
hsCRP	-0.18	0.03
Pericardial Fat Volume	-0.16	0.05

Conclusions: Physical activity is independently associated with insulin resistance, vascular disease and endothelial function, and may be a low-risk adjuvant to decreasing co-morbidities in HIV+ adults. Further studies should examine long-term effects of physical activity on markers of cardiometabolic health and inflammation in this population.

WEDNESDAY, FEBRUARY 25, 2015

Session P-P5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Cardiovascular Risk Prediction

746 Cumulative HIV Care Measures Highly Associated With Acute Myocardial Infarction

Jorge L. Salinas[1]; Christopher T. Rentsch[2]; Vincent C. Marconi[1]; Janet Tate[3]; Adeel A. Butt[4]; Matthew S. Freiberg[4]; Matthew B. Goetz[5]; Maria Rodriguez-Barradas[6]; Amy Justice[3]; David Rimland[1]

[1]Emory University, Atlanta, GA, US; [2]Atlanta VA Hospital, Decatur, GA, US; [3]Yale University, New Haven, CT, US; [4]University of Pittsburgh, Pittsburgh, PA, US; [5]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US; [6]Baylor College of Medicine, Houston, TX, US

Background: After accounting for established risk factors, people living with HIV (PLWHIV) have a 50-75% greater risk of acute myocardial infarction (AMI) than uninfected individuals. Several underlying causes for this association have been suggested including ongoing chronic inflammation, immune suppression, and a greater burden of anemia, renal disease, liver disease, and hepatitis C infection. While many of these factors have been studied in a cross-sectional manner, few have considered the association of cumulative HIV care measures with AMI among PLWHIV. We hypothesized that measuring these factors in a cumulative way would be associated with AMI incidence.

Methods: Retrospective cohort study including PLWHIV starting antiretroviral therapy (ART) in the Veterans Aging Cohort Study Virtual Cohort (VACS VC) from 2000-2009. The impact of baseline, time-updated and cumulative measures of HIV viremia, CD4 count and the VACS Index were modeled. Cumulative measures were captured starting 6 months after ART initiation until AMI event, death, last clinic visit or censor date (December 31, 2009) and calculated as follows:

1) Copy Years viremia (CYV)= Area under the curve of HIV viral load (VL) measures.

2) CD4 Years (CD4Y)= Area under the curve of CD4 measures.

3) VACS Index years (VISY)= Area under the VACS Index curve.

Areas under the curve were calculated using the trapezoidal rule. The VACS Index score was calculated using age, HIV-1 RNA, CD4, aspartate and alanine transaminases, hemoglobin, platelet count, creatinine and known hepatitis C infection. An online calculator is available (http://vacs.med.yale.edu). The primary outcome was incident AMI determined using Medicare and VA ICD9 codes. Multi-variable proportional hazard (PH) models were fit for time to AMI.

Results: 12,131 patients were included in the analysis. Separate PH models were fit for different measures of VL, CD4 and the VACS Index (basal, time-updated and cumulative) and results are presented in table 1. While all three cumulative measures predicted the studied outcome, VCY≥63, 000 copy-years/mL (HR=4.17; 95%CI=3.59-4.85) and CD4Y<750 cell-years/mm^3 (HR=5.61; 95%CI=4.56-6.90); patients with higher VACS Index score-years had the highest risk of AMI (VISY≥250; HR=40.56; 95%CI=33.25-49.47).

HIV viral load measures				CD4 measures				VACS Index measures			
	Person-years	AMIs	Adjusted HR*		Person-years	AMIs	Adjusted HR**		Person-years	AMIs	Unadjusted HR***
Baseline VL (copies/mL)				Baseline CD4 (cells/ mm^3)				Baseline VACS Index score			
<75,000	23,301	84	1	<200	22,582	80	1.45 (1.30-1.61)	<50	25,827	77	1
75,000+	23,749	84	1.12 (1.01-1.24)	200+	24,581	87	1	50+	15,888	68	2.79 (2.51-3.10)
Time-updated VL (copies/mL)				Time-updated CD4 (cells/mm^3)				Time-updated VACS Index score			
<500	47,957	156	1	<200	8,710	43	7.31 (6.29-8.49)	<25	26,830	59	1
500-4,199	2,586	8	1.85 (1.53-2.24)	200-349	9,587	45	2.20 (1.85-2.62)	25-39	13,037	50	2.43 (2.01-2.94)
4,200-38,999	2,783	18	2.85 (2.42-3.36)	350-499	11,120	39	1.42 (1.17-1.73)	40-59	8,857	47	6.78 (5.72-8.03)
39,000+	3,678	13	5.12 (4.52-5.8)	500+	27,362	69	1	60+	7,898	45	35.20 (30.31-40.88)
Time-updated viremia (VCY) (copy-years/mL)				Time-updated CD4-years (CD4Y) (cell-years/ mm^3)				Time-updated VACS Index score-years (VISY)			
<1,200	6,325	49	1	<750	4,608	45	5.61 (4.56-6.90)	<75	10,518	55	1
1,200-2,999	17,690	51	1.25 (1.02-1.54)	750-1,749	9,632	58	2.27 (1.86-2.77)	75-149	11,536	58	5.91 (5.04-6.94)
3,000-62,999	16,172	47	1.97 (1.67-2.32)	1,750-2,999	12,968	41	1.50 (1.22-1.84)	150-249	13,641	42	14.87 (12.37-17.88)
63,000+	16,818	48	4.17 (3.59-4.85)	3,000+	29,569	52	1	250+	20,362	46	40.56 (33.25-49.47)
Abbreviations: AMI: Acute myocardial infarction; HR: Hazard ratio; VL: Viral load; VCY: Viremia copy-years; VACS: Veterans Aging Cohort Study											
*Adjusted for age and baseline CD4 count **Adjusted for age and baseline HIV viral load ***The VACS Index includes age, VL, CD4, aspartate and alanine transaminases (AST, ALT), hemoglobin, platelets, creatinine and hepatitis C infection											

Table 1. Multivariable Cox Proportional Hazards analyses of factors associated with time to Acute Myocardial Infarction among patients starting Initial ART regimens in the VACS Virtual Cohort; 2000-2009.

Conclusions: Cumulative measures of viral load, CD4 count and VACS Index provide added information about risk of AMI, of these, VACS Index is the most comprehensive.

747 Cardiovascular Disease Risk Prediction in the HIV Outpatient Study (HOPS)

Angela M. Thompson-Paul[1]; **Kenneth A. Lichtenstein**[2]; Carl Armon[3]; Kate Buchacz[1]; Rachel Debes[3]; Joan S. Chmiel[4]; Frank J. Palella[4]; Stanley C. Wei[1]; Jacek Skarbinski[1]; John T. Brooks[1]

[1]US Centers for Disease Control and Prevention, Atlanta, GA, US; [2]National Jewish Health, Denver, CO, US; [3]Cerner Corporation, Vienna, VA, US; [4]Northwestern University, Feinberg School of Medicine, Chicago, IL, US

Background: HIV infection is associated with an increased risk of cardiovascular disease (CVD); however, it is unknown if commonly used CVD risk prediction tools accurately predict risk in HIV-infected persons. In this analysis, we examined four CVD risk prediction equations to determine if they accurately estimate events and predict risk events in a large diverse cohort of HIV-infected adults in the United States.

Methods: We analyzed longitudinal data on HIV Outpatient Study (HOPS) participants in care at 10 U.S. clinic sites as of 30 September 2013 who met the following criteria: had at least one year of follow-up after 1 January 2002, enrolled in the HOPS no later than 1 October 2010, had at least one total cholesterol measurement, and at least two systolic blood pressure measurements at baseline. We applied four CVD risk equations to the HOPS data to estimate 10-year CVD risk, and using Harrell's *C*-statistic assessed their predictive ability to discriminate patients who did vs. did not experience incident CVD events. Incident CVD events were defined for each risk equation are as follows: 1) Framingham Point Score (FPS)– myocardial infarction (MI), fatal coronary heart disease (CHD), stroke; 2) Pooled Cohort Equation (PCE) - MI, stroke, coronary artery disease (CAD); 3) Systematic COronary Risk Evaluation (SCORE) for low-risk populations – fatal MI, stroke, peripheral vascular disease, CAD; and 4) the Data Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study equations - MI, sudden death, CAD, stroke, and death from other CHD.

Results: There were 2392 participants with a median age of 43 years; 76% were male, 50% were non-Hispanic white, and 87% were antiretroviral experienced at baseline. Common co-morbid conditions included hypertension (50%), diabetes (10%), and high cholesterol (17%). In this cohort, 204 incident CVD events occurred during a median follow-up time of 6.5 years. All equations underestimated 10-year CVD risk to a variable degree (Table 1). The FPS, PCE, and D:A:D equations showed moderate discrimination (C-statistic range, 0.68 to 0.72), whereas SCORE showed poor discrimination (C-statistic=0.59).

HOPS participants (n=2,392)	10-Year CVD Risk Estimation			
	FPS	PCE	SCORE	D:A:D
C-statistic*	0.71	0.71	0.57	0.72
Expected events (E)	126	147	19	193
Observed events (O)	149	178	23	256
Ratio E/O	0.85	0.83	0.83	0.75
p-value	0.002	<0.001	0.02	<0.001

Abbreviations: FPS, Framingham Point Score; PCE, Pooled Cohort Equation; SCORE, Systematic COronary Risk Evaluation; D:A:D, Data Collection on Adverse Effects of Anti-HIV Drugs. * Harrell's C-statistic assessed the ability of each prediction model to discriminate patients who did vs. did not experience incident CVD events.

Comparison of 10-year cardiovascular disease (CVD) risk estimation and discrimination in four CVD risk calculators in HIV-infected adults from the HIV Outpatient Study (HOPS).

Conclusions: The four risk prediction equations underestimated the 10-year risk of CVD in our large, diverse cohort of HIV-infected adults. To better estimate CVD risk in HIV-infected persons in the U.S., additional risk factors, such as immunologic or virologic status may need to be considered.

748 Incidence and Risk of Myocardial Infarction (MI) by Type in the NA-ACCORD

Daniel R. Drozd[1]; Mari M. Kitahata[1]; Keri N. Althoff[2]; Jinbing Zhang[2]; Susan R. Heckbert[1]; Matthew J. Budoff[3]; Frank J. Palella[4]; Daniel B. Klein[5]; Richard D. Moore[6]; Heidi M. Crane[1]

[1]University of Washington, Seattle, WA, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]University of California Los Angeles, Los Angeles, CA, US; [4]Northwestern University, Chicago, IL, US; [5]Kaiser Permanente Northern California, Hayward, CA, US; [6]Johns Hopkins University, Baltimore, MD, US

Background: HIV-infected persons may be at increased risk for cardiovascular disease (CVD) and MI, but the role of HIV in the pathogenesis of MI is unclear. The Universal Definition of MI (UDMI) classifies MIs by underlying pathophysiology into classic *primary* (type 1) MIs due to atherothrombotic coronary plaque rupture and *secondary* (type 2) MIs resulting from supply-demand mismatch caused by a heterogeneous set of clinical conditions including sepsis and cocaine-induced vasospasm. In the general population, primary MIs are more common than secondary MIs. Prior studies in HIV have not classified the type of MI and therefore, have examined primary and secondary MIs as a single endpoint, which may limit their ability to define the contribution of HIV to CVD and primary MI risk. We determined the incidence of adjudicated primary MIs distinct from secondary MIs and examined baseline risk factors for primary MIs.

Methods: MIs were centrally adjudicated in 7 NA-ACCORD clinical cohorts between 1996-2010 in patients who screened positive and classified according to the UDMI; primary events included invasive cardiac interventions (CABG, stent placement). Incidence rates (IRs) per 1,000 person-years (PY), adjusted incidence rate ratios (aIRRs), and 95% confidence intervals ([,]) were estimated using Poisson regression adjusted at baseline for sex, race/ethnicity, HIV risk group, year of enrollment, cohort, ever smoked, hypertension (HTN), diabetes (DM), dyslipidemia, chronic kidney disease (CKD), CD4 count, and HIV RNA (viral load); age was time-updated.

Results: There were 24,919 patients who experienced 262 primary and 205 secondary MIs in 95,728 PYs of follow-up: primary MI IR=2.74 [2.42, 3.09] and secondary MI IR=2.14 [1.87, 2.46]. Significant predictors of primary MI included age, HTN, DM, dyslipidemia, smoking, stage 4/5 CKD, and CD4 count (Table 1). Sepsis (33%), cocaine (8%), respiratory failure (5%), and hypertensive emergency (4%) combined accounted for 50% of all secondary MIs.

Table 1. Adjusted rate ratios (aIRR) and 95% confidence intervals for primary MI

	aIRR [95% CI]
Age	
<40	1.00
40-49	**3.42 [2.06, 5.68]**
50-59	**5.14 [3.05, 8.66]**
60-69	**9.96 [5.66, 17.53]**
Hypertension	**1.92 [1.45, 2.55]**
Diabetes mellitus	**2.01 [1.39, 2.89]**
Ever smoker	**2.02 [1.38, 2.94]**
Dyslipidemia	**1.75 [1.32, 2.32]**
Stage 4/5 CKD	**7.73 [3.05, 19.59]**
CD4 (cells/mL)	
<200	1.00
200-349	**0.63 [0.44, 0.90]**
≥350	**0.66 [0.49, 0.88]**
HIV viral load (copies/mL)	
<200	1.00
201-9,999	1.23 [0.88, 1.71]
10,000-99,999	**1.54 [1.06, 2.24]**
≥100,000	1.17 [0.71, 1.92]

Conclusions: Traditional CVD risk factors and immunosuppression significantly predict primary MIs. The high rate of secondary MIs emphasizes the need for greater clarity in outcome ascertainment in studies seeking to study the pathogenic role of HIV in CVD. Future analyses will examine the complex longitudinal relationship between primary MIs and HIV-specific factors including CD4 count, viral load, and ART.

749LB Abacavir Use and Risk for Myocardial Infarction in the NA-ACCORD

Frank J. Palella[1]; Keri N. Althoff[2]; Richard Moore[3]; Jinbing Zhang[2]; Mari Kitahata[4]; Stephen J. Gange[2]; Heidi M. Crane[4]; Daniel R. Drozd[4]; John T. Brooks[5]; Richard Elion[6]

[1]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]Johns Hopkins University, Baltimore, MD, US; [4]University of Washington, Seattle, WA, US; [5]US Centers for Disease Control and Prevention, Atlanta, GA, US; [6]George Washington University, Washington, DC, US

Background: Whether abacavir (ABC) exposure contributes to myocardial infarction (MI) risk remains unclear. Large observational studies, including D:A:D, found ABC use associated with nearly 2-fold increased MI risk; other studies have found no association. We evaluated MI risk associated with recent ABC use among patients in the largest North American cohort study: NA-ACCORD.

Methods: Incident MIs from seven U.S. cohorts of HIV-infected persons in NA-ACCORD were centrally adjudicated using MESA criteria and classified per the Universal Definition of MI as either atherothrombotic (type 1) or demand ischemia (type 2). Adults who were ABC-naïve at entry were included and followed until MI, death, one year after last CD4 or HIV RNA measurement, or 12/31/2010. Recent ABC use was defined as prescription within the prior 6 months. We used pooled logistic regression models to estimate adjusted hazard ratios and 95% confidence intervals for MI risk associated with recent ABC use adjusting for demographics, cigarette smoking, diabetes, hypertension, renal impairment, high total cholesterol, high triglycerides, statin use, CD4, previous protease inhibitor use, calendar year, and cohort.

Results: 16,733 adults contributed 301 incident MIs and 64,607 person-years of follow up. Persons who initiated ABC were significantly more likely to have traditional MI risk factors (older age, smoking, hypertension, low HDL, high total cholesterol, and black race) and factors linked to inflammation (history of IDU, HCV infection, CD4 <200 cells/mm^3, detectable HIV RNA, and history of AIDS). Without adjustment, the MI risk associated with recent ABC use was 1.88 (1.35, 2.60). In an adjusted model similar to that used in the D:A:D study, the MI risk associated with recent ABC use was 1.71 (1.11, 2.64). In a model that further adjusted for traditional MI and HIV-related risk factors measured prior to ABC use as confounders of the ABC/MI relationship, the MI risk associated with recent ABC use was 1.34 (0.96, 1.88); results stratified by MI type were similar.

Conclusions: We found an increased risk for MI associated with recent ABC use that diminished in magnitude and statistical significance after adjusting for traditional and HIV-associated MI risk factors, many of which were significantly more prevalent in ABC users. Further analyses are underway to account for potential time-dependent confounding of risks for MI.

750 HIV-Infected Veterans and the New ACC/AHA Cholesterol Guidelines: Got Statins?

Meredith E. Clement[1]; Lawrence Park[1]; Ann Marie Navar-Boggan[1]; Nwora L. Okeke[1]; Michael Pencina[1]; Pamela Douglas[1]; Susanna Naggie[1]

[1]Duke University, Durham, NC, US; [2]Duke University, Durham, NC, US; [3]Duke University, Durham, NC, US

Background: Cardiovascular disease, an HIV-associated non-AIDS related (HANA) condition, is an emerging threat to people living with HIV; thus, appropriate primary and secondary prevention is critical. In November 2013 updated guidelines for cholesterol treatment from the American College of Cardiology and the American Heart Association (ACC/AHA) substantially expanded recommendations for statin use among the general population for cardiovascular disease (CVD) prevention compared to the prior Adult Treatment Panel (ATP-III) guidelines. How these new recommendations impact adults with HIV-infection is unknown.

Methods: We used the Veterans Affairs (VA) Clinical Case Registry (CCR), one of the largest clinical databases of HIV-infected patients worldwide, to determine the impact of the new the new cholesterol guidelines on statin recommendations for HIV-infected veterans. Electronically available laboratory, medication, and comorbidity data from 2008 to 2010 were used to assess statin recommendations under the ATP-III and the 2013 AHA/ACC guidelines among male patients aged 40 to 75 years. Descriptive statistics are presented comparing the proportion of adults recommended under each guideline.

Results: 13293 male veterans with HIV-infection met inclusion criteria for the analysis. The average age was 54.6 years. Cardiovascular disease was present in 8.2% and diabetes in 15.4%. Of 13293 veterans, 5185 (39.0%) had been prescribed statin therapy (32.2% for primary prevention and 6.8% for secondary prevention). Overall, 11.6% of adults not previously eligible for statin therapy under ATP-III were newly recommended under ACC/AHA guidelines, with 7085 (53.3%) veterans recommended for statin therapy under the ATP-III guidelines compared to 8630 (64.9%) under the ACC/AHA guidelines. The majority of the increase in statin eligibility was in adults recommended for primary prevention; with 9.1% newly recommended based on 10-year risk score, 1.7% newly recommended based on diabetes, and 0.8% newly recommended based on presence of CVD.

	ATP-III	ACC/AHA
Already on Statin		
Primary prevention	4286 (32.2%)	4286 (32.2%)
Secondary prevention (CVD)	899 (6.8%)	899 (6.8%)
Subtotal	**5185 (39.0%)**	**5185 (39.0%)**
New Statin Recommended		
Primary prevention	1803 (13.5%)	3244 (24.4%)
LDL>190	70 (0.5%)	70 (0.5%)
Diabetes	248 (1.9%)	475 (3.6%)
10-yr Risk Score	1485 (11.2%)	2699 (20.3%)
Secondary Prevention (CVD)	97 (0.7%)	201 (1.5%)
Subtotal	**1900 (14.3%)**	**3445 (25.9%)**
No Statin Recommended		
Primary prevention	6104 (45.9%)	4663 (35.1%)
Diabetes	384 (2.9%)	157 (1.2%)
10-yr Risk Score	5720 (43.0%)	4506 (33.9%)
Secondary Prevention	104 (0.8%)	0
Subtotal	**6208 (46.7%)**	**4663 (35.1%)**
Total	**13293 (100%)**	**13293 (100%)**

Conclusions: In our study population of HIV-infected veterans, application of the new ACC/AHA cholesterol guidelines resulted in an approximate 12% absolute increase in the proportion of patients for whom statin therapy is indicated. The increased recommended use of statins is primarily related to risk assessed by the 10-year risk score of cardiovascular disease. It will be important to assess the benefit of this expanded prevention measure prospectively.

751 Evaluation of the ACC/AHA CVD Risk Prediction Algorithm Among HIV-Infected Patients

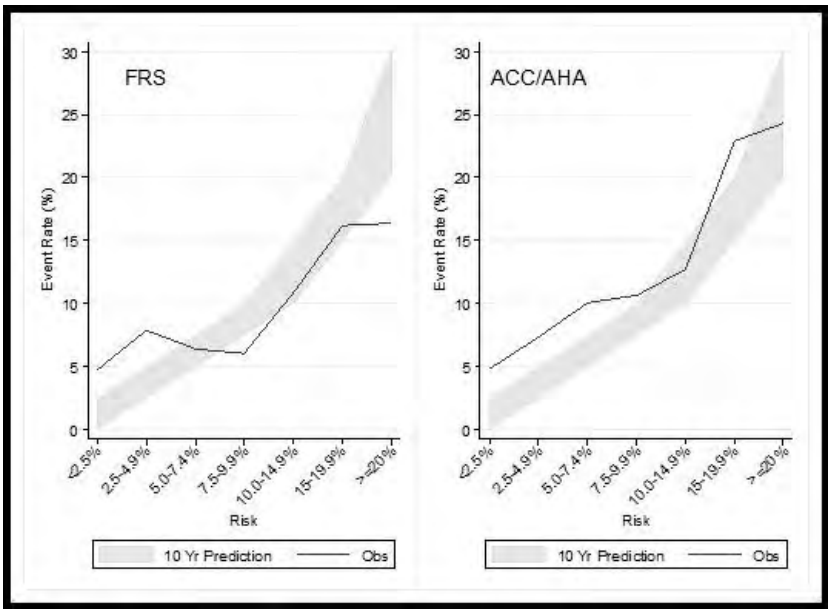
Susan Regan[2]; James B. Meigs[2]; Joseph Massaro[3]; Ralph B. D'Agostino[3]; Steven Grinspoon[2]; **Virginia A. Triant**[2]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Boston University, Boston, MA, US; [4]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

Background: The 2013 American College of Cardiology (ACC)/ American Heart Association (AHA) cardiovascular disease (CVD) risk prediction algorithm (Pooled Cohorts Equations) has not previously been evaluated in HIV populations.

Methods: Framingham Risk Scores (FRS) and ACC/AHA risk scores were calculated for patients in a longitudinal HIV clinical care cohort during a 3-year interval ending January 1, 2009. Patients were not eligible if they were under age 18, had expired prior to January 1, 2009, were missing relevant data to populate the risk score, or had undergone a relevant outcome event prior to the date of risk score calculation. CVD risk was considered high if 10-year predicted risk of the relevant outcome event was ≥10 percent for FRS and ≥7.5 percent for ACC/AHA. Outcome events were coronary heart disease (CHD) for FRS and atherosclerotic CVD (ASCVD) for ACC/AHA.

Results: The FRS was calculated for 2270 patients, with a median follow-up time of 6.3 years, and the ACC/AHA risk score was calculated for 2152 patients, with a median follow-up time of 6.2 years. Risk scores were discordant in 17 percent of patients, with the ACC/AHA score only predicting high risk in 10 percent and the FRS only predicting high risk in 7 percent. In comparisons of these discordant subgroups, patients classified as high-risk by ACC/AHA but low-risk by FRS were older (median age 56 for ACC/AHA high vs. 48 for FRS high) and more likely to be female (68% vs. 0%), diabetic (52% vs. 6%) and black (22% vs. 12%) but less likely to be smokers (44% vs. 66%) than those low-risk by ACC/AHA and high-risk by FRS. Actual event rates were estimated and compared with predicted rates. As shown in the figure, actual 6-year event rates were similar to 10-year predicted rates for the FRS and were similar to or exceeded predicted rates for the ACC/AHA risk score.



Conclusions: Our findings suggest that CVD risk prediction scores designed for the general population, and particularly the new ACC/AHA risk score, may underestimate risk for HIV-infected patients. Accurate CVD risk prediction is an important component of the long-term management of chronic disease complications in HIV.

TUESDAY, FEBRUARY 24, 2015

Session P-P6 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Biomarkers and Atherosclerosis

752 IL-6 and CD8 Senescence Independently Associate With Atherosclerosis in Treated HIV

Denise C. Hsu[1]; Zonghui Hu[1]; Courtney Carroll[2]; Kristinalisa Maka[2]; Adam Rupert[3]; Steven Deeks[2]; S. C. Kalapus[2]; Priscilla Hsue[2]; Irini Sereti[1]

[1]National Institute of Allergy and Infectious Diseases, Bethesda, MD, US; [2]University of California San Francisco, San Francisco, CA, US; [3]Leidos Biomedical Research, Inc, Frederick, MD, US

Background: Increased cardiovascular (CV) risk persists among patients with treated HIV disease, and chronic immune activation is thought to contribute to this excess risk. Carotid intima-media thickness (CIMT) assesses atherosclerotic burden and predicts future CV events. We studied the immunologic correlates of CIMT in patients on ART with suppressed viral load (VL).

Methods: Cryopreserved mononuclear cells and plasma from the SCOPE study were used to evaluate T-cell and monocyte activation by flow cytometry and soluble markers of inflammation/coagulation by ELISA-based methods. CIMT was measured by high resolution ultrasound. Mean CIMT was calculated as the average of 12 segments (near and far wall of the common, internal, and bifurcation region of the right and left carotid arteries). Plaque was defined as a focal region of IMT>1.5mm. Associations between CIMT and immunologic markers were assessed by Spearman's rank correlation and multivariate regression adjusting for traditional CV risk factors and CD4 count. Associations between the presence of plaque and immunologic markers were evaluated by Wilcoxon test.

Results: Participants (N=132) were on ART with VL <75 copies/mL, 93% male, 67% Caucasian. The median age was 48 yrs, 32% were on anti-hypertensive drugs, 41% were on cholesterol lowering drugs, 7% had diabetes, 7% had CVD and 26% were smokers. The median CD4 was 525 cells/μL. The mean CIMT was 1.04 mm and plaque was present in 54% of patients.

In multivariate regression adjusting for traditional CV risk factors and CD4 count, higher levels of plasma IL-6 (P<0.01) and CCR5 expression on monocytes (P<0.01) were associated with thicker common carotid-IMT. In addition, higher levels of plasma IL-6 (P=0.03), and higher % of CD57+ cells in CD28-CD8+ T cells (P=0.04) were correlated with thicker mean-CIMT.

Levels of D-dimer, CRP, sCD14, sCD163, HLA-DR+CD38+CD8+T cells and CD16+ monocytes were not associated with common carotid or mean CIMT or plaque after adjusting for traditional CV risk factors and CD4 count.

Conclusions: In patients on ART with suppressed VL, higher plasma IL6 and CCR5 expression on monocytes and higher % of CD57+ cells in CD28-CD8+T cells were independently associated with thicker CIMT after adjusting for CVD risk factors and CD4 count. Dysfunction of innate immune cells and CD8 T cell senescence likely contribute to atherosclerosis in the setting of treated and suppressed HIV.

753 sCD163 Correlates With IMT and Macrophages in Aorta and Heart With HIV Infection

Joshua A. Walker[1]; Graham A. Beck[1]; Andrew D. Miller[2]; Tricia H. Burdo[1]; Kenneth C. Williams[1]

[1]Boston College, Chestnut Hill, MA, US; [2]Cornell University, Ithaca, NY, US

Background: HIV-associated mortality is decreased due to effective ART. HIV+ individuals have a two-fold greater risk of cardiovascular complications. Increased risk is likely due to chronic inflammation and virus. We have shown by FDG-PET imaging, increased monocyte/macrophage accumulation in the ascending aorta with HIV infection correlates with the numbers of non-calcified, vulnerable plaques. SIV-infected monkeys had increased inflammatory cardiac macrophages and fibrosis. We asked whether macrophage activation, accumulation, and soluble CD163 correlate with intima-media thickness (IMT) of the ascending aorta and fibrosis in left ventricular tissues with HIV infection.

Methods: Matched plasma and tissue sections of left ventricle and aorta from ten HIV- and ten HIV+ individuals were obtained from the NDRI and NNTC. Levels of sCD163, a monocyte/macrophage activation marker were measured by ELISA. Matched aorta and left ventricle were scored based on the degree of inflammation, degeneration, and fibrosis. IMT of the aorta was quantified visually after an elastic stain. Levels of fibrosis in the left ventricle were assessed using a modified Massons trichrome stain. Sections were stained with antibodies recognizing CD163+, CD68+, MAC387+, and CD206+ macrophages, and CD3+ T-lymphocytes.

Results: Levels of sCD163 in plasma were significantly increased 62.3% in HIV+ individuals compared to controls (P<0.05, t-test). We found a 49.7% increase in the IMT of the ascending aorta in HIV+ individuals compared to uninfected. In matched left ventricular sections we found a 59.7% increase in the level of fibrosis. Levels of sCD163 significantly correlated with increased IMT as well as increased fibrosis in HIV+ individuals compared to uninfected (r=.51, r=.68, respectively p<0.05). Examination of matched tunica intima of the aortas and left ventricular sections from HIV- and HIV+ show increased numbers of CD163+ (57.2%, 47.3%), CD68+ (59.5%, 55.0%), MAC387+ (56.3%, 53.5%) and CD206+ (32.3%, 38.9%). We found positive correlations between IMT and the numbers of macrophages present in the tunica intima, and fibrosis in the left ventricle (r=.68, r=.74, respectively p<0.05)

Conclusions: These data suggest a role for monocyte/macrophage activation and accumulation in the development of cardiovascular pathology measured by IMT of the ascending aorta and fibrosis in the heart with HIV infection.

754 Non-Classical Monocytes Predict Progression of Carotid Intima-Media Thickness

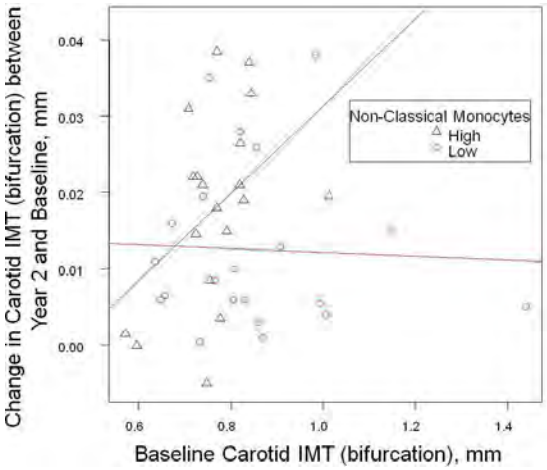
Dominic C. Chow[1]; Jamie M. Kagihara[1]; Guangxiang G. Zhang[1]; Scott A. Souza[1]; Brooks I. Mitchell[1]; Beau K. Nakamoto[1]; Kalpana J. Kallianpur[1]; Robert J. Matyas[2]; Lishomwa C. Ndhlovu[1]; Cecilia M. Shikuma[1]

[1]University of Hawaii, Honolulu, HI, US; [2]Kaiser Permanente, Honolulu, HI, US

Background: Chronic HIV-1 infection is characterized by systemic immune activation and inflammation and may contribute to cardiovascular disease (CVD) risk. We assessed relationships of monocyte [MO] subsets, CD38+HLA-DR+CD8+ T cells and various cytokines, to HIV immune dysregulation and carotid intima-media thickness (cIMT).

Methods: We conducted a longitudinal analysis from a cohort study of CVD risk in HIV-infected subjects aged $\geq$ 40 years on stable antiretroviral therapy (ART) $\geq$ 6 months. Fasting blood was assessed for glucose, insulin and lipids. Peripheral blood mononuclear cells (PBMCs) were phenotyped by flow cytometry for MO subsets [classical MO (CD14++CD16-), intermediate (CD14++CD16+), non-classical ($CD14_{low}$/+CD16++)] and CD38+HLA-DR+ CD8+ T cells at baseline. Plasma biomarker multiplexing was performed. Soluble biomarkers included sE-selectin, sVCAM-1, sICAM-1, MMP-9, MPO, tPA-1, CRP, SAA, SAP, IL-1β, IL-6, IL-8, IL-10, TNF-α, MCP-1, VEGF, IFN-γ, and NT ProBNP. High resolution B-mode ultrasound images of the right carotid bifurcation were obtained at baseline and year 2. Changes in cIMT were assessed. Pearson correlation and linear regression were used for statistical analysis.

Results: We studied 50 subjects: 84% male, median age 49 (Q1,Q3: 46, 56) years, median CD4 count 461 (317,578) cells/mm^3, with HIV RNA$\leq$50 copies/ml in 84%. Change in cIMT correlated positively with log values of non-classical MO count (r=0.37, p=0.020) and percentage (r=0.36, p=0.025), MCP-1 (r=0.42, p=0.0024) and TNF-a (r=0.30, p=0.036). Non-classical MO percentage correlated with MCP-1 (r=0.32, p=0.045). Among the monocyte subsets, only non-classical MO predicted cIMT at the bifurcation independent of age, BMI, smoking, CD4 percent and presence of HIV RNA (β=0.13, p=0.040). Additionally, if study subjects were split by the non-classical MO percentage median value (7.33%) to High and Low levels, then the baseline cIMT value itself tended to predict the cIMT change at year 2 at the High level (R^2=19.6%), but not at Low level of non-classical MO (R^2=0.2%).



Conclusions: HIV immune dysregulation is associated with elevated levels of non-classical MO. Increased non-classical MO subsets parallel increases in pro-inflammatory cytokines such as MCP-1. Non-classical MO predict progression of cIMT at the bifurcation in HIV-infected individuals on suppressive ART independent of traditional cardiometabolic and HIV immunovirologic factors, and may contribute to CVD.

755 TMAO and HIV-Associated Atherosclerosis

Arjun Sinha[1]; Yifei Ma[1]; Rebecca Scherzer[2]; Courtney Carroll[1]; Steven Deeks[3]; Peter Ganz[1]; Priscilla Hsue[1]

[1]San Francisco General Hospital, San Francisco, CA, US; [2]San Francisco VA Medical Center, San Francisco, CA, US; [3]University of California San Francisco, San Francisco, CA, US

Background: HIV-infected individuals are at increased risk for atherosclerosis. The underlying mechanisms may include alterations in gut microbial flora, leading to immune activation. Trimethylamine-N-oxide (TMAO) is metabolized by intestinal microbiota from dietary lipids. In uninfected persons, TMAO levels are associated with cardiovascular events. The objective of this study was to investigate factors associated with TMAO and determine if TMAO is associated with subclinical atherosclerosis in HIV-infected individuals.

Methods: TMAO levels in 83 HIV-infected individuals were compared to an external cohort of uninfected individuals referred for cardiac catheterization for suspected coronary artery disease (CAD) from Tang et al (NEJM 2013; 368:1575-1584). Carotid intima-media thickness (IMT) was assessed using high resolution ultrasound. Multivariable analysis was performed to identify the relationship between TMAO and mean IMT.

Results: Compared to controls, the HIV group was younger (50 ± 10 vs 63 ± 11 yrs), primarily male (94% vs 64%), and had lower rates of DM (11% vs 32%) and HTN (46% vs 72%). Nearly 75% of the HIV cohort were on anti-retroviral therapy (ARVs). Median TMAO level in the HIV cohort was 3.7 μM (IQR 2.5-6.3), which was identical to that in uninfected controls with CAD (3.7, IQR 2.4-6.2). In adjusted analysis, age, cigarette smoking, triglycerides, and current ARV use were independently associated with higher TMAO levels in the HIV group. Viral load and CD4 count were not associated with TMAO levels. The mean carotid IMT was 0.105 ± 0.035 mm in HIV-infected individuals. TMAO per doubling was associated with 9% greater mean carotid IMT in univariate analysis (p=0.002), but the association weakened in the adjusted model (+4%, p=0.14). Age, Latino/Asian race, HTN, cigarette smoking, total cholesterol, and lipodystrophy were also associated with greater IMT.

Conclusions: Despite being younger and having fewer traditional risk factors, HIV-infected patients had similar TMAO levels as uninfected individuals with CAD. While viral load and CD4 count were not predictive of higher TMAO levels, current ARV use was. In conclusion, these results suggest that TMAO levels are elevated and may be associated with mean carotid IMT in HIV-infected individuals. Future studies will need to establish whether these elevated circulating TMAO levels in HIV patients are associated with an increased risk of cardiovascular events.

756 Impaired Cardiac Strain and Biomarkers of Immune Activation in HIV

Colleen Hadigan[1]; **Julia Purdy**[1]; Diana Thiara[1]; Louisa Howard[1]; Chia-Ying Liu[1]; Fabio Raman[1]; Sabrina Mangat[1]; Christopher Sibley[2]; David Bluemke[1]

[1]National Institutes of Health (NIH), Bethesda, MD, US; [2]Oregon Health and Sciences University, Portland, OR, US

Background: Chronic HIV infection is associated with an increased risk of cardiovascular disease (CVD). Subclinical cardiac dysfunction can be assessed through MRI measurements of cardiac strain and myocardial fibrosis. In order to investigate the underlying etiology of CVD in HIV, we performed cardiac MRI in conjunction with biomarkers of inflammation and immune activation in a cohort of HIV+ adults without known CVD.

Methods: This is a prospective cross-sectional study of 95 HIV+ adults and 30 age, sex, race-matched healthy controls. Myocardial fibrosis (quantified as extracellular volume index) and regional cardiac strain were measured by MRI. Laboratory determinations included serologic biomarkers of inflammation, coagulation, and immune activation (e.g. C-reactive protein [CRP], D-dimer, pro-brain natriuretic peptide [pro-BNP], monocyte chemoattractant protein-1 [MCP-1], lipopolysaccharide binding protein [LBP], tissue inhibitor of metalloproteinase-1 [TIMP-1]).

Results: Radial strain and epicardial-endocardial circumferential strain were significantly decreased in HIV+ compared to controls (Table 1). Among the HIV+ group, radial strain impairment was strongly correlated with increased levels of MCP-1 (r=-0.43, p<0.0001), pro-BNP (r=-0.28, p<0.01), TIMP-1 (r=-0.28 p=0.009) and LBP (r=-0.21, p=0.03). In a multivariable regression adjusting for smoking and age, HIV status (p=0.04) and increased MCP-1 levels (p=0.0002) remained significant independent predictors of impaired radial strain. Myocardial fibrosis was also increased in the HIV+ group compared to controls, and correlated with decreased epicardial-endocardial circumferential strain (r=0.22, p=0.03).

Table 1. Results

Inflammation Biomarkers	HIV (n=95)	Control (n=30)	p-value
D-Dimer (ug/mL FEU)	0.32±0.25	0.43±0.31	0.09
CRP (mg/L)	3.6±5.7	3.9±5.3	0.8
Pro-BNP (pg/mL)	57.6±133.7	31.6±32.5	0.09
MCP-1 (pg/mL)	473±249	321±221	0.003
LBP (ng/mL)	437±233	410±224	0.6
TIMP-1 (ng/mL)	12.3±61.1	10.1±46.3	0.03
Cardiac Strain and Fibrosis MRI			
Systolic Circumferential Strain (%)	-15.8±2.7	-16.4±2.5	0.31
Systolic Circumferential Strain Rate	-93.9±18.9	-100.4±23.7	0.23
Systolic Radial Strain (%)	21.7±8.6	30.5±14.2	0.004
Systolic Radial Strain Rate	99.7±41.0	121.3±49.6	0.048
Systolic Epicardial-Endocardial Circumferential Strain (%)	7.0±2.5	8.5±2.8	0.02
Myocardial Fibrosis Index	0.28±0.04	0.26±0.03	0.02

Conclusions: HIV-infected subjects demonstrate subclinical impairment in systolic function and this is associated with markers of chronic immune activation, inflammation and tissue remodeling. Similar to patients with chronic heart failure, increased levels of MCP-1, a chemokine important in the regulation of macrophage migration and a marker of immune activation, was a strong independent predictor of impairment in cardiac function. LBP, an acute phase protein made in response to LPS, and TIMP-1, a marker of tissue remodeling, were also associated with impaired cardiac strain. Our findings indicate that subclinical impairment in cardiac strain tracks with markers of chronic inflammation and immune activation, which may serve as targets for future therapeutic strategies to optimize long-term cardiovascular health in persons living with HIV.

TUESDAY, FEBRUARY 24, 2015

Session P-P7 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Endothelial Functions and Cerebral Vasoreactivity

757 Role of Angiopoietin 1, Angiopoietin 2, and Endothelial Function in HIV

Mark L. Dela Cruz[1]; Yifei Ma[1]; Rebecca Scherzer[1]; Alan Wu[2]; Kristinalisa Maka[1]; Steven Deeks[1]; Peter Ganz[1]; Priscilla Hsue[1]

[1]*University of California San Francisco, San Francisco, CA, US;* [2]*Blood Systems Research Institute/University of California San Francisco, San Francisco, CA, US*

Background: HIV-infected patients have increased risk for cardiovascular disease (CVD). The underlying mechanism likely involves impaired endothelial function, a precursor of atherosclerosis. Endothelial homeostasis is promoted by the Tie2 receptor system through its agonist, angiopoietin-1 (Ang1) while its antagonist, the inflammatory protein angiopoietin-2 (Ang2), promotes endothelial activation. We hypothesized that HIV infection is associated with decreased Ang1 and increased Ang2 levels, leading to impaired endothelial function.

Methods: We performed a cross-sectional analysis of Ang1 and Ang2 serum levels by ELISA, among 89 HIV-infected individuals, and 46 uninfected controls. Endothelial function was measured by flow-mediated dilation of the brachial artery (FMD). Generalized linear regression models and Spearman correlations were used to determine the association of HIV to Ang1/Ang2 levels and FMD.

Results: The median age was 49 yrs and 87% were male. Compared to controls, HIV-infected individuals were younger (median age 45 yrs vs 53 yrs, p=0.03), less likely to be male (82% vs 98%, p=0.03), and more likely to have renal disease (eGFR<60) (13.5% vs 2.2%, p=0.04). Forty-seven (53%) of the HIV-infected individuals were effectively treated and suppressed with antiretroviral therapy (ART). Compared to controls, Ang1 levels were lower in HIV-infected individuals (median 2219 pg/ml, IQR 1022 to 4280, p= 0.01) while Ang2 levels were higher (median 2147 pg/ml, IQR 1617 to 3106, p=0.06). After adjustment for traditional risk factors, Ang1 levels remained significantly lower in HIV subjects compared to controls (-43.8%, p=0.018) while Ang2 levels were no longer different (p=0.65). Individuals on effective ART had 29% lower Ang1 levels compared to controls in adjusted analysis (p=0.01) and lower Ang1 levels were independently associated with impaired FMD (p<0.001).

Conclusions: Circulating Ang1 levels are reduced among HIV-infected individuals compared to controls, even in subjects on effective ART. Lower Ang1 is independently associated with impaired endothelial function. These data suggest that HIV infection leads to an imbalance between Ang1 and Ang2, resulting in endothelial dysfunction through the Tie2 receptor system. Our findings reveal a potential new target for mitigating CVD risk in the setting of treated HIV infection.

758 HIV-Infected Persons With Type 2 Diabetes Have Evidence of Endothelial Dysfunction

Malene Hove[1]; Julie C. Gaardbo[3]; Hedda Hoel[3]; Lillian Kolte[2]; Allan Vaag[1]; Jan Gerstoft[1]; Henrik Ullum[1]; Marius Troseid[3]; Susanne D. Poulsen[1]

[1]*Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark;* [2]*Hvidovre Hospital, University Hospital of Copenhagen, Hvidovre, Denmark;* [3]*Oslo University Hospital, Ullevål, Norway*

Background: Increased incidence of cardiovascular diseases (CVD) in HIV-infected persons compared to the general population has been described. Likewise, Type 2 diabetes (T2D) is an independent risk factor for CVD. T2D is characterized by endothelial dysfunction. Endothelial dysfunction has been suggested as possible cause to increased risk of CVD in HIV infection. Little is known about the combined effect of HIV infection and T2D on endothelial function. We hypothesized an additive effect of HIV infection and T2D on endothelial dysfunction.

Methods: A cross-sectional study was performed including 50 HIV-infected persons on cART and with HIV RNA < 200 copies/mL (n=25 with T2D (HIV+T2D+), n=25 without T2D (HIV+T2D-)), and 50 HIV-negative persons (n=22 with T2D (HIV-T2D+) and n=28 without T2D (HIV-T2D-). Groups were matched on age and sex, and groups of HIV-infected patients were matched on CD4 cell count (672 cells/mL vs 663 cells/mL). Assymetric dimethylarginine (ADMA) and Trimethylamine-N-oxid (TMAO) were used as markers of endothelial dysfunction and analyzed in snap-frozen EDTA-plasma using high performance liquid chromatography and Stable isotope dilution, respectively. Differences between groups were analyzed using one-way ANOVA and *t* test. Data are given as mean (95%CI).

Results: HIV+T2D+ had elevated ADMA (0.67 μM (0.63-0.72) compared to HIV+T2D- (0.60 μM (0.57 - 0.64) p=0.017), HIV-T2D+ (0.57 μM (0.51-63) p=0.008) and HIV-T2D- (0.55 μM (0.52- 0.58) p<0.001) (FIG 1). In contrast, no differences in TMAO level between the four groups were found(HIV+T2D+: 7.51μM (4.28-10.75), HIV+T2D-: 5.58μM (3.55-7.61), HIV-T2D+: 4.56μM (3.89- 5.22) and HIV-T2D- 7.07μM (3.63-10.52)). However, we found a positive correlation between ADMA and TMAO in HIV+T2D+ and HIV+T2D- (p=<0.001, r=0.524).

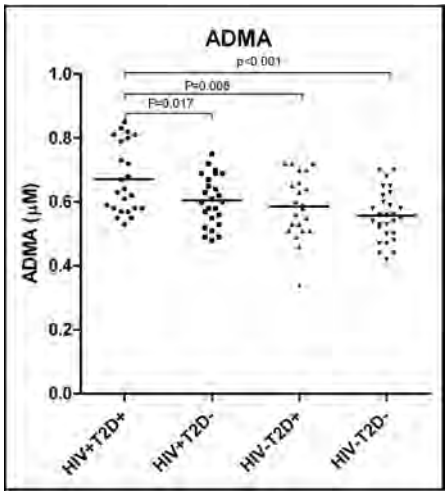


FIG 1

Conclusions: Evidence of endothelial dysfunction was found in HIV-infected persons with T2D compared to HIV-infected persons without T2D. Thus, Our data indicate an addictive effect of HIV infection and T2D on endothelial dysfunction possibly leading to elevated risk of CVD. This underlines the clinical importance of effective CVD prevention strategies in this group of patients.

759 Unique Circulating MicroRNA Profiles and Endothelial Function in HIV Infection

Venkata A. Narla[1]; Nirav Bhakta[2]; Jane E. Freedman[3]; Kahraman Tanriverdi[3]; Kristinalisa Maka[1]; Steven Deeks[2]; Peter Ganz[1]; Priscilla Hsue[1]

[1]San Francisco General Hospital, University of California San Francisco, San Francisco, CA, US; [2]University of California San Francisco, San Francisco, CA, US; [3]University of Massachusetts Medical School, Worcester, MA, US

Background: MicroRNAs (miRs) are non-coding RNAs that regulate gene expression and can serve as biomarkers given their stability in blood and characteristic expression in various diseases. The role of extracellular miRs as potential biomarkers in HIV infection and HIV-associated cardiovascular disease (CVD) has not been described.

Methods: We analyzed the expression of 192 plasma-derived miRs from 69 HIV-infected individuals and 24 uninfected controls using Taqman miR Expression Assays and a high throughput RT-PCR instrument (Fluidigm). We also examined the association between 68 circulating miRs and flow-mediated dilatation of the brachial artery (FMD), a physiologic measure of endothelial function and a strong predictor of future CVD events, using Firefly Bioworks hydrogel particles-based miR assays. Comparisons were made using Student's t-test, Wilcoxon rank-sum test, ANOVA, and Kruskal-Wallis test where appropriate, and false discovery rate was applied.

Results: HIV–infected individuals and controls were matched in age, gender, and traditional risk factors. The median age was 46 years (IQR 40 to 54) and 91% were men. Among the HIV patients, 72.5% were on antiretroviral therapy and 64% had an undetectable viral load. Twenty-nine miRs were differentially expressed in the plasma of HIV-infected individuals compared to controls ($p<0.05$ and FDR <0.15). In particular, miRs-29c, 146b, 223, and 382 have reported intracellular roles in HIV latency, and miRs-126, 145, and let-7 have been shown to be differentially expressed in coronary artery disease (CAD) among individuals without HIV. Levels of miRs-34a, 27b, and 1183 varied with different FMD quartiles ($p<0.05$). Thirty-eight miRs were differentially expressed in the serum of HIV-infected individuals from the low FMD quartile compared with the top FMD quartile ($p<0.05$; thirty miRs had FDR<0.05 and eight miRs had FDR< 0.07). In this profile, in particular, miRs-1, 133a, 133b, 208a, 208b, 499, 145, and 155 have been shown to be differentially expressed in CAD patients without HIV.

Conclusions: We demonstrate a unique miR expression profile of 29 miRs in HIV-infected individuals, as well as a unique profile of 38 miRs in HIV-infected individuals with high CVD risk and impaired endothelial function. These miR profiles may be useful in identifying HIV-infected individuals who are at increased risk for CVD, may help elucidate the underlying mechanism of HIV-associated CAD, and may be therapeutic targets for new anti-HIV drugs and CVD drugs.

760 Cerebral Vasoreactivity Is Impaired in Virally Suppressed HIV-Infected Individuals

Felicia C. Chow[1]; Claire Mills[1]; Nerissa Ko[1]; Courtney Carroll[1]; Richard Price[1]; Steven Deeks[1]; Farzaneh A. Sorond[2]; Priscilla Y. Hsue[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US

Background: Rates of vascular outcomes, including stroke, are higher in HIV-infected individuals than in age-matched uninfected controls. Endothelial dysfunction and accelerated atherosclerosis related to chronic inflammation and immune activation may contribute to HIV-associated cardiovascular risk. The mechanisms underlying increased cerebrovascular risk in HIV infection have not been investigated. We compared cerebral vasoreactivity (VR), a measure of intracranial endothelial function associated with cerebrovascular injury, by HIV status. We also evaluated the effect of HIV-specific factors on cerebral VR.

Methods: Cross-sectional study of bilateral cerebral VR, assessed using the transcranial Doppler carbon dioxide (CO_2) challenge test, in HIV-infected participants and uninfected controls recruited from SCOPE (Study of the Consequences of the Protease Inhibitor Era). All HIV-infected participants were on a stable antiretroviral therapy (ART) regimen for at least 24 weeks with undetectable plasma HIV RNA level. Cerebral VR was defined as the percentage change in mean flow velocity per unit change in end-tidal CO2. We used mixed effects multivariate linear regression models adjusted for age, race and clinically relevant variables chosen by forward stepwise regression to determine the association between HIV and cerebral VR and between HIV-specific factors and cerebral VR. We included a random person effect to account for within-person correlation of bilateral measurements.

Results: 65 HIV-infected and 28 uninfected control participants matched by age and sex were studied. Median age was 57 years, 96% were men and 28% were non-white race. Mean duration of HIV infection was 20 years. Diabetes mellitus (12 vs. 0%, p=0.052), aspirin (49 vs. 21%, p=0.012), statin (48 vs. 11%, p=0.001) and marijuana use (48 vs. 21%, p=0.018) were more prevalent among HIV-infected participants than uninfected controls. In a multivariate model, HIV infection, non-white race and select traditional vascular risk factors were associated with worsened cerebral VR (Table). Among HIV-infected individuals, we did not find a statistically significant effect of recent or nadir CD4 count, duration of HIV infection or ART class on cerebral VR.

Table: Effect of HIV infection on cerebral vasoreactivity

	HIV-infected (n=65) + HIV-uninfected (n=28) Total n=93, Total observations (left + right sides) n=175	
	Difference in mean cerebral vasoreactivity (95% CI)	P value
HIV infection	-0.67 (-1.08 to -0.26)	0.001
Age (per 10-year increase)	-0.11 (-0.32 to +0.10)	0.31
Race (non-white versus white)	-0.68 (-1.10 to -0.27)	0.001
Diabetes mellitus	-0.87 (-1.56 to -0.18)	0.013
Aspirin use	+0.38 (-0.04 to +0.80)	0.076
Statin use	+0.36 (-0.07 to +0.78)	0.10
Methamphetamine use	-1.12 (-1.91 to -0.34)	0.005
Alcohol use (for each additional drink per month)	+0.01 (-0.001 to +0.02)	0.083

Conclusions: Treated and virally suppressed HIV infection is an independent risk factor for impaired cerebral VR, a marker of subclinical cerebrovascular dysfunction. Further investigation into the etiology of cerebrovascular injury in chronic, well-controlled HIV infection is merited.

TUESDAY, FEBRUARY 24, 2015

Session P-Q1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Inflammation: Biomarkers and Relationship to Outcomes

761 IL-6 Is a Stronger Predictor of Clinical Events Than hsCRP or D-Dimer in HIV Disease

Álvaro H. Borges[1]; Jemma L. O'Connor[2]; Andrew N. Phillips[2]; James D. Neaton[3]; Birgit Grund[4]; Jacqueline Neuhaus[3]; Michael Vjecha[7]; Alexandra Calmy[5]; Kersten K. Koelsch[6]; Jens D. Lundgren[1]
INSIGHT SMART and ESPRIT Study Groups

[1]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [2]University College London, London, United Kingdom; [3]University of Minnesota, Minneapolis, MN, US; [4]University of Minnesota, Minneapolis, MN, US; [5]Geneva University Hospitals, Geneva, Switzerland; [6]University of New South Wales, Sydney, Australia; [7]Veterans Affairs Medical Center, Washington, DC, US

Background: High-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6) and D-dimer have been linked to risk of death and of many clinical outcomes during HIV infection. However, the strength of associations these biomarkers have with different types of clinical events is not well understood.

Methods: Participants receiving standard of care in the control arms of 2 HIV trials (SMART and ESPRIT) with biomarkers measured at baseline were followed from study entry to ascertain all-cause death, non-AIDS death, progression to AIDS, cardiovascular disease (CVD) and non-AIDS-defining malignancies (NADM). Marginal Cox models were used to model multiple unordered events and to test for equal effects of biomarkers on different clinical endpoints. HRs (95% CIs) stratified by study of each endpoint for $\log_2$-transformed hsCRP, IL-6 and D-dimer levels (i.e., per 2 fold higher) were calculated using the following Cox models: (1) unadjusted; (2) adjusted for demographics, ART use, nadir and baseline CD4, HIV RNA, prior AIDS and CVD, diabetes and HBV/HCV. We then recalculated HRs for IL-6 and D-dimer using models (3) that included both biomarkers simultaneously and HRs for hsCRP using a model also adjusted for D-dimer.

Results: There were 19000 person-years of follow-up among 4304 participants (median age 42y, median CD4 526, 77% men), including 157 all-cause deaths, 117 non-AIDS deaths, 101 progressions to AIDS, 121 CVD and 99 NADM (Table). In multivariable analyses, independent associations between IL-6 and clinical endpoints were strongest for non-AIDS death (1.71; 1.43-2.04) and similar for all-cause death (1.56; 1.33-1.84), CVD (1.35; 1.12-1.62) and NADM (1.30; 1.06-1.61). When compared to hsCRP, IL-6 was found to be more strongly associated with all outcomes investigated both in univariable and multivariable models. Likewise, IL-6 was a stronger predictor for most outcomes than D-dimer, except for progression to AIDS. We found evidence of heterogeneity in the predictive ability of IL-6 for different endpoints ($p<0.001$), but not of hsCRP ($p=0.15$) or D-dimer ($p=0.20$).

Table: SMART and ESPRIT

Hazard Ratios (95% CI) Associated with Baseline Biomarkers (per one $\log_2$ [i.e. per 2 fold higher] increment)

Cohort: All control Patients

Biomarker		All-cause deaths[1]		Non-violent, non-accidental non-AIDS deaths[2]		Progression to AIDS[3]		Cardiovascular Disease[4]		Non AIDS-defining malignancies[5]		P-value for chi-square; marginal Cox models
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	
hsCRP	Model 1[a]	**1.29 (1.18-1.41)**	<.001	**1.33 (1.20-1.47)**	<.001	**1.12 (1.00-1.25)**	0.048	**1.20 (1.09-1.24)**	<.001	**1.17 (1.05-1.31)**	0.006	N/A
	Model 2[b]	**1.29 (1.17-1.42)**	<.001	**1.30 (1.16-1.46)**	<.001	1.07 (0.94-1.21)	0.329	1.11 (0.99-1.24)	0.069	**1.16 (1.02-1.32)**	0.025	N/A
	Model 3[c]	**1.25 (1.13-1.38)**	<.001	**1.27 (1.13-1.42)**	<.001	1.02 (0.89-1.16)	0.783	1.09 (0.97-1.22)	0.154	**1.15 (1.01-1.31)**	0.035	0.20[e]
IL-6	Model 1[a]	**1.84 (1.62-2.09)**	<.001	**1.94 (1.69-2.24)**	<.001	**1.39 (1.17-1.67)**	<.001	**1.51 (1.30-1.77)**	<.001	**1.43 (1.21-1.71)**	<.001	N/A
	Model 2[b]	**1.64 (1.41-1.92)**	<.001	**1.77 (1.50-2.10)**	<.001	**1.32 (1.07-1.62)**	0.009	**1.40 (1.17-1.67)**	<.001	**1.31 (1.07-1.61)**	0.008	N/A
	Model 3[c]	**1.56 (1.33-1.84)**	<.001	**1.71 (1.43-2.04)**	<.001	1.22 (0.98-1.51)	0.076	**1.35 (1.12-1.62)**	0.002	**1.30 (1.06-1.61)**	0.014	**0.0005[e]**
D-dimer	Model 1[a]	**1.45 (1.28-1.65)**	<.001	**1.43 (1.23-1.65)**	<.001	**1.38 (1.18-1.62)**	<.001	**1.29 (1.11-1.49)**	<.001	**1.19 (1.01-1.41)**	0.033	N/A
	Model 2[b]	**1.32 (1.14-1.52)**	<.001	**1.30 (1.10-1.53)**	0.002	**1.35 (1.12-1.63)**	0.001	**1.22 (1.04-1.43)**	0.014	1.09 (0.91-1.31)	0.342	N/A
	Model 3[d]	**1.22 (1.05-1.43)**	0.011	1.17 (0.98-1.40)	0.079	**1.31 (1.08-1.59)**	0.007	1.16 (0.98-1.36)	0.088	1.03 (0.86-1.25)	0.731	0.15[e]
	No events	157		117		101		121		99		
	No patients	4,304										

P < 0.05 for HRs (95% CI) written with bold letters
[a] unadjusted associations, stratified by study
[b] adjusted for demographics (age, sex, race and BMI), ART use, nadir and baseline CD4+ cell count, baseline HIV RNA, prior AIDS and cardiovascular disease, diabetes mellitus and HBV/HCV co-infection
[c] as in (b) and adjusted for D-dimer
[d] as in (b) and adjusted for IL-6
[e] p-value from marginal Cox models testing for heterogeneity of associations between each biomarker and endpoints 2-5

Conclusions: The upstream inflammatory marker IL-6 is a stronger predictor of a variety of non-AIDS clinical events than the downstream inflammatory marker hsCRP or the hypercoagulation marker D-Dimer. IL-6 predicts fatal non-AIDS events more strongly than CVD or NADM. Evaluation of the clinical benefits from interventions able to reduce IL-6 levels in HIV is warranted.

762 Persistent Inflammation on ART Is Associated With Poor Nutritional Recovery in Zambia

George Praygod[2]; Meridith Blevins[1]; Susannah Woodd[3]; Andrea Rehman[3]; Jeremiah Kidola[2]; Henrik Friis[4]; Paul Kelly[5]; Douglas Heimburger[1]; Suzanne Filteau[3]; **John Koethe**[1]

[1]Vanderbilt University, Nashville, TN, US; [2]National Institute of Medical Research, Mwanza, United Republic of Tanzania; [3]London School of Hygiene & Tropical Medicine, London, United Kingdom; [4]University of Copenhagen, Copenhagen, Denmark; [5]University Teaching Hospital, Lusaka, Zambia

Background: Persistent, elevated systemic inflammation accelerates HIV-associated weight loss, but the effects of inflammation on nutritional rehabilitation after the start of antiretroviral therapy (ART) are not well understood. We assessed the relationships between serum C-reactive protein (CRP) and changes in lean body mass over the first 12 weeks of ART among malnourished adults in the completed Nutritional Support for Africans Starting Antiretroviral Therapy (NUSTART) trial.

Methods: HIV-infected, ART-eligible Zambian and Tanzanian adults with body mass index < 18.5 kg/m^2 were randomized to receive a lipid-based nutritional supplement fortified with high-dose vitamins and minerals versus supplement alone from referral for ART to 6 weeks after starting treatment. Anthropometry and bioelectrical impedance analysis

(BIA) were performed at recruitment and after 6 and 12 weeks of ART, and serum CRP was measured at recruitment and 6 weeks. The relationships between CRP and changes in body composition measurements were assessed using linear regression models adjusted for age, sex, CD4 count, hemoglobin, trial arm, study site, tuberculosis treatment at ART initiation, and baseline CRP and anthropometric values.

Results: 838 trial participants who had baseline and 6 week CRP measurements were included in this analysis. Median age was 35 years, 51% were female, and median CD4 count was 135 cells/μL. Median CRP was high at recruitment (61 mg/l; IQR 14, 160) and lower, although still abnormally elevated, after 6 weeks of ART (34 mg/l; IQR 12, 94). A one-log reduction in CRP at 6 weeks was associated with increased mid-upper-arm circumference (0.45 cm, p<0.001), calf circumference (0.38 cm, p<0.001), waist circumference (0.98 cm, p<0.001) and BIA fat-free mass (0.58 kg, p<0.001), but CRP was not associated with BIA fat mass. Trial arm was not a mediating variable in any of these relationships. The anthropometric and fat-free mass gains persisted after completion of the supplement, and the largest increases in lean mass at 12 weeks were observed in patients with moderate-to-high baseline CRP and lower 6 week CRP.

Conclusions: Larger reductions in CRP shortly after ART initiation were associated with greater increases in lean body mass, which is a marker of nutritional rehabilitation and may impact future cardiometabolic disease risk. Further studies are needed to understand the directionality of the observed the relationships.

763 Smoking and Obesity May Partially Explain the Inflammation and Morbidity Association

Supriya Krishnan[1]; Ronald Bosch[1]; Benigno Rodriguez[2]; Peter W. Hunt[3]; Cara C. Wilson[4]; Steven Deeks[3]; Michael M Lederman[2]; Alan Landay[5]; Carey Lumeng[6]; Allan Tenorio[7]

[1]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, US; [2]Division of Infectious Diseases and HIV Medicine, Case Western Reserve University School of Medicine, Cleveland, OH, US; [3]Positive Health Program, Dept of Medicine, San Francisco General Hospital, San Francisco, CA, US; [4]Division of Infectious Diseases, Univ of Colorado Hospital, Aurora, CO, US; [5]Department of Immunology and Microbiology, Rush Univ Medical Center, Chicago, IL, US; [6]Univ of Michigan Medical School, Department of Pediatrics, Ann Arbor, MI, US; [7]Department of Medicine, Rush University Medical Center, Chicago, IL, US

Background: As in the general population, increased central obesity and smoking are correlated with higher levels of soluble inflammatory markers in HIV+ virally suppressed patients. We previously reported that high levels of IL-6, sTNFR-1 and 2 and D-dimer were associated with an occurrence of a non-AIDS event. Understanding the pathophysiology of inflammation in HIV and biologic pathways between inflammation and non-AIDS morbidities may inform therapeutic strategies for HIV-infected populations.

Methods: A previously described case-control study (143 cases with non-AIDS morbidities including MI/stroke/non-AIDS malignancy/death, 315 matched controls) examined HIV+ adults from the ACTG-ALLRT cohort who were ART naïve at entry, received a modern ART regimen, and were virally suppressed (<400 cp/ml) at year 1 of ART. Stored plasma at year 1 was tested for IL-6, IP-10, sTNFR-I & –2, sCD14 and D-dimer. Conditional logistic regression was used to examine if each soluble marker was independently associated with non-AIDS morbidities adjusting for other soluble markers (singly), waist circumference (WC, cm) and smoking (# of cigs/day) at year 1. WC and smoking were included because they correlated with the soluble markers in a previous analysis and are known risk factors for the outcome in the general population.

Results: IL-6 was independently associated with non-AIDS outcomes even after separately adjusting for sTNFR-1 and 2, D-dimer, IP-10 and sCD14 (all p≤0.001). In contrast, the associations for D-dimer and sCD14 were no longer significant when IL-6 was included in the model. Both sTNFR-1 and sTNFR-2 remained independently associated with non-AIDS outcomes even after adjusting for IL-6. In a model that included WC and smoking, the OR for IL-6 was attenuated from 1.82 to 1.54 (Table 1). In contrast, adjusting for WC and smoking only slightly altered the OR for sTNFR-1 and 2 (Table 1).

Table 1. Odd ratios and 95% confidence intervals for IL-6, sTNFR-1 and sTNFR-2.

	OR per 1 IQR increase (95% CI)	p-value
IL-6	1.82 (1.37, 2.44)	<0.001
IL-6 adjusted for STNFR-1	1.59 (1.17, 2.16)	0.003
IL-6 adjusted for STNFR-2	1.63 (1.21, 2.20)	0.001
sTNFR-1	1.74 (1.31, 2.33)	<0.001
STNFR-1 adjusted for IL-6	1.48 (1.09, 2.01)	0.013
sTNFR-2	1.70 (1.27, 2.27)	<0.001
STNFR-2 adjusted for IL-6	1.48 (1.09, 2.01)	0.013
IL-6 adjusted for WC	1.66 (1.19, 2.32)	0.003
IL-6 adjusted for smoking	1.70 (1.26, 2.28)	<0.001
IL-6 adjusted for WC and smoking	1.54 (1.09, 2.18)	0.015
sTNFR-1 adjusted for WC and smoking	1.73 (1.21, 2.47)	0.003
sTNFR-2 adjusted for WC and smoking	1.71 (1.18, 2.47)	0.004

Conclusions: Among the six soluble markers evaluated, IL-6, sTNFR-1 and sTNFR-2 measured during viral suppression appear to be robust predictors of and may be part of distinct pathways leading to subsequent non-AIDS outcomes. The IL-6 association was independent of obesity and smoking; however the effect was attenuated by 15% suggesting that obesity and smoking may play a role in some IL-6 related pathways leading to an increased risk of non-AIDS outcomes. These findings further support efforts to identify the effects of reducing obesity and smoking on residual inflammation.

764 Infectious and Noninfectious Multimorbidity Among HIV Clinic Clients in the African Cohort Study

Julie Ake[1]; Jonah Maswai[2]; Francis Kiweewa[3]; Lucas Maganga[4]; Milton Omondi[5]; Babajide Keshinro[6]; Lindsay Hughes[1]; Victor G. Valcour[7]; Christina Polyak[1]
RV 329 AFRICOS Study Team

[1]US Military HIV Research Program, Bethesda, MD, US; [2]KEMRI/Walter Reed Project, Kericho, Kenya; [3]Makerere University Walter Reed Project, Kampala, Uganda; [4]Mbeya Medical Research Centre, Mbeya, United Republic of Tanzania; [5]KEMRI/Walter Reed Project, Kisumu, Kenya; [6]Walter Reed Program - Nigeria, Abuja, Nigeria; [7]University of California San Francisco (UCSF), San Francisco, CA, US

Background: The frequency and complexity of multimorbidity in the increasingly treated African HIV epidemic is not comprehensively described.

Methods: The African Cohort Study (AFRICOS) prospectively enrolls adult HIV clinic clients and uninfected adults at 10 PEPFAR supported facilities in Kayunga, Uganda; South Rift Valley and Kisumu West, Kenya; Mbeya, Tanzania and Abuja, Nigeria. We evaluated infectious comorbidities (ICOs) at baseline: HBV, HCV and syphilis by screening serologies, pulmonary TB by Xpert MTB/RIF, and cryptococcosis by serum CrAg if CD4≤200. Baseline noninfectious comorbidities (NICOs) included elevated blood pressure (SBP>138 or DBP>79), impaired fasting glucose (IFG) (>99 mg/dl), renal insufficiency (GFR<60 mL/min), hypercholesterolemia (total cholesterol >199 mg/dl), anemia (hemoglobin <11 mg/dl), and cognitive impairment (International HIV Dementia Scale < 1.5 SD below the mean). We compared those with no comorbidities to those with ≥2 comorbidities using descriptive statistics and investigated determinants of NICOs employing multivariate Poisson regression.

Results: From January 2013 to August 2014, 899 HIV infected adults enrolled in Kayunga (22%), South Rift Valley (41%), Kisumu West (15%), Mbeya (14%), and Abuja (7%). Participants were 60% female with mean age 40.5 years and mean CD4 count 419 cells/mm^3. Among the 73% taking antiretroviral therapy (ART), mean ART duration was 4.1 years, 68% were suppressed to < 50 copies/mL, and 78% had exposure to thymidine analogues. Rates of smoking and IDU were low (3.4% and 0.2%). Reactive serologies for hepatitis B, C, and syphilis were identified in 5.2%, 4.4% and 1.3%. Sixteen (1.8%) had positive Xpert assays and 2 (0.7%) had cryptococcal antigenemia. The most common NICOs

were elevated blood pressure (17.7%), anemia (13.1%) and IFG (11.4%). 48% had at least one comorbidity and 14% had ≥2. 12% had ≥1 ICO and 41% had ≥1 NICO. Those with ≥2 comorbidities had significantly higher age (p<0.0001), lower CD4 count (p=0.004) and higher body mass index (BMI) (p=0.01) than those without comorbidity. Multivariate regression revealed independent association of age (p<0.0001), BMI (p=0.02), CD4 count (p=0.03) and female gender (p=0.02) with total NICOs.

Conclusions: The cohort demonstrates considerable HIV associated multimorbidity in a largely rural African context. Body mass and CD4 count are potentially modifiable predictors of NICOs. Future analyses will prospectively assess the impact of expanded ART eligibility on these outcomes.

TUESDAY, FEBRUARY 24, 2015

Session P-Q2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Bone Metabolism and ART: Mechanisms and Outcomes

765 Bone Metabolism and Tenofovir: Evidence of Direct Effect on Calcium-Sensing Receptor

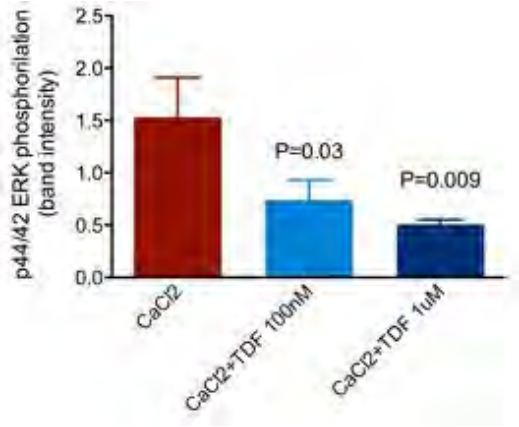
Paolo Bonfanti[2]; Caterina Brasacchio[3]; Chiara Molteni[2]; Barbara Menzaghi[1]; Laura Soldati[3]; Tiziana Quirino[1]; Stefano Mora[4]

[1]Busto Arsizio Hospital, Busto Arsizio, Italy; [2]A. Manzoni Lecco Hospital, Lecco, Italy; [3]Department of Health Sciences, University of Milan, Milan, Italy; [4]San Raffaele Scientific Institute, Milan, Italy

Background: Bone health impairment is a common finding in HIV-infected patients on antiretroviral treatment. Bone mineral derangement is the result of bone metabolism alterations, associated to some antiretroviral agents. We previously reported high serum parathyroid hormone (PTH) concentration in patients on HAART containing tenofovir disoproxil fumarate (TDF). Hyperparathyroidism in these patients was not always sustained by a reduction in vitamin D concentration. We thus hypothesized a direct inhibitory effect of TDF on the calcium sensing receptor (CaR), leading to hyperparathyroidism, responsible for the bone complication.

Methods: Human embryonic kidney cells transfected with CaR wild-type gene (HEK-293-CaR WT) were used. Cells were grown in standard conditions (37°C, 5%CO2) and the activity of CaR was assessed after stimulation with different concentrations of CaCl2 (0.5mM-1mM-3mM-5mM) and TDF (100nM-1μM) (kindly provided by Gilead Sciences, Inc). We evaluated by western blot and Image J software phospho-p44/42 ERK expression levels as a marker of CaR activity.

Results: Calcium alone lead to the activation of CaR with all concentrations of CaCl2 tested. However, the highest CaR activity was detected at 3mM CaCl2 and this concentration was used for the subsequent stimulation analyses. We observed a marked reduction of CaR activity by adding TDF to cell cultures (Figure). The stimulation by CaCl2 3mM and TDF 100nM lead to decrease of 52% CaR activity, whereas the stimulation by CaCl2 3mM and TDF 1μM reduced the activity by 67%. Both reductions were statistically significant (P=0.03, and P=0.009, respectively).



Conclusions: The stimulation of CaR by its natural ligand, calcium, leads to the suppression of PTH secretion by the parathyroid glands. Our experiments demonstrated that TDF is able to inhibit the stimulation of CaR in a dose-dependent manner. Hyperparathyroidism observed in TDF-treated patients may be therefore promoted by the direct effect of the drug on CaR.

766 Bone Turnover on DRV/r + Either RAL or TDF/FTC as First-Line ART: NEAT 001 / ANRS 143

Jose I Bernardino[1]; Amanda Mocroft[2]; Laura Richert[3]; Abdel Babiker[4]; Antonio Buño[1]; Antonella Castagna[5]; Pierre-Marie Girard[6]; Genevieve Chene[3]; Jose R Arribas[1]; François Raffi[7]

[1]Hospital Universitario La Paz. IdiPAZ, Madrid, Spain; [2]University College London, London, United Kingdom; [3]University of Bordeaux, Bordeaux, France; [4]MRC Clinical Trials Unit at University College London, London, United Kingdom; [5]San Raffaele Scientific Institute, Milan, Italy; [6]Hospital St Antoine and Inserm, Paris, France; [7]Université Nantes, Nantes, France

Background: Darunavir/ritonavir (DRV/r) + raltegravir (RAL) was associated with significantly less bone mineral density (BMD) loss over 96 weeks than DRV/r + tenofovir/emtricitabine (TDF/FTC) in first-line treatment of HIV-infected patients. Changes in bone and inflammatory biomarkers could partially explain differences in BMD loss.

Methods: NEAT001/ANRS143 is a randomised 1:1, open-label trial comparing DRV/r + RAL or TDF/FTC in 805 ART naive HIV-infected adults. 146 patients were included in the bone substudy (70 and 76) prior to randomised treatment allocation. We measured 25-OH vit D and a variety of bone and inflammatory biomarkers at baseline and 48 weeks. BMD was measured by DXA at baseline, 48 and 96 weeks. Changes in bone and inflammatory markers were evaluated by parametric comparisons. Associations between baseline values and changes in BMD at both 48 and 96 weeks were explored by linear and logistic regression.

Results: 133 patients had at least one biomarker measured at randomisation; 91.7% male, 12.0% black, median age 39 yrs, median BMI 23.1 Kg/m^2, 41.4% were current smokers. Osteopenia/osteoporosis was evidenced at baseline in 24/5 patients in lumbar spine and in 19/1 patients in total hip. 21 patients had a previous history of fracture. There were no significant differences between treatment arms in biomarkers at baseline. Significantly greater changes in bone biomarkers were seen at 48 week in the DRV/r + TDF/FTC arm but there were no differences in changes in inflammatory markers (Table). In multivariate analysis, baseline level of P1NP ≤ 44.7 ng/mL was associated with a total hip BMD loss ≧ 5% at 48 weeks (OR 10.76; 95% CI 1.29, 90.2) and femoral neck BMD loss ≧ 5% at 96 weeks (OR 4.63; 95% CI 1.29, 46.6). Baseline osteopontin level ≤ 5423 pg/mL was associated with a lumbar spine BMD loss ≥ 5% at 96 weeks (OR 0.17; 95% CI 0.09, 0.68).

	Mean absolute change from baseline to 48 weeks					P
	DRV/r + RAL		DRV/r + TDF/FTC		Difference between arms	
	N	Mean (95% CI)	N	Mean (95% CI)	Mean (95% CI)	
Osteocalcin ng/mL	38	4.8 (2.3, 7.3)	47	8.6 (6.6, 10.6)	3.7 (0.6, 6.8)	0.024
BSAP µg/L	38	2.4 (0.8, 4.0)	45	6.7 (5.1, 8.3)	4.3 (1.9, 6.7)	<0.001
P1NP ng/mL	38	12 (3.8, 20.2)	46	25.8 (20.1, 31.5)	13.7 (4.1, 23.3)	0.007
Osteoprotegerin pg/mL	38	63.6 (17.3, 109.9)	46	-29.5 (-81.8, 22.8)	-93 (-164.3, -21.7)	0.013
Serum CTX-1 ng/mL	38	0.08 (0.0, 0.2)	45	0.31 (0.20, 0.40)	0.2 (0.10, 0.30)	<0.001
RANKL pmol/L	12	-0.28 (-0.79, 0.23)	13	-0.15 (-0.37, 0.07)	0.13 (-0.40, 0.66)	0.64
Osteopontin pg/mL	38	-9.3 (-1117, 1098)	46	451 (-983, 1884)	460 (-1411, 2331)	0.63
Urine CTX-1 /creatinine ratio µg/mmol	59	59.0 (26.1, 91.9)	65	111.9 (78.4, 145.4)	52.9 (5.9, 99.9)	0.03
25-OH vit D ng/mL	38	4.4 (0.9, 7.9)	45	6.1 (2.4, 9.8)	1.7 (-3.4, 6.8)	0.51
IL-1β pg/mL	37	0.11 (0.01, 0.21)	45	-0.08 (0.02, 0.18)	-0.03 (-0.17, 0.12)	0.71
IL-6 pg/mL	38	-0.20 (-2.0, 1.6)	46	0.2 (-0.9, 1.3)	0.4 (-1.6, 2.4)	0.71
TNF-α pg/mL	35	-2.0 (-0.2,- 3.8)	44	1.8 (1.2, 2.4)	0.3 (-1.4, 1.9)	0.73

Conclusions: Compared to the nucleos(t)ide sparing regimen of DRV/r + RAL, patients treated with DRV/r + TDF/FTC had significantly greater changes in bone turnover biomarkers. Measuring bone biomarkers before starting ART could help to identify those patients at greater risk of BMD loss ≥ 5% on ART.

767 Tenofovir Replacement in Patients With Osteoporosis Increased Sclerostin Levels

Eugenia Negredo[3]; Adolfo Díez-Pérez[2]; Pere Domingo[4]; Nuria Pérez-Álvarez[6]; Mar Gutierrez[4]; Gracia Mateo[4]; Jordi Puig[1]; Patricia Echeverria[1]; Anna Bonjoch[1]; Bonaventura Clotet[5]

[1]Lluita Contra la Sida Foundation, Germans Trias i Pujol University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; [2]Hospital del Mar-IMIM, Universitat Autònoma de Barcelona and RETICEF, Instituto Carlos III Madrid, Barcelona, Spain; [3]Lluita Contra la Sida Foundation, Germans Trias i Pujol University Hospital, Universitat Autònoma de Barcelona, Universitat de Vic–Universitat Central de Catalunya, Barcelona, Spain; [4]Santa Creu i Sant Pau Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; [5]Lluita Contra la Sida Foundation, Germans Trias i Pujol University Hospital, Universitat Autònoma de Barcelona, Irsicaixa Foundation, Germans Trias i Pujol University Hospital, Barcelona, Spain; [6]Lluita Contra la Sida Foundation, Germans Trias i Pujol University Hospital, Universitat Autònoma de Barcelona, Statistics and Operations Research Department, Universitat Politècnica de Catalunya, Barcelona, Spain

Background: Tenofovir is one of the antiretroviral drugs involved in accelerated bone mineral density (BMD) loss.

Methods: We recently published changes in 54 virologically suppressed patients during a tenofovir-containing regimen and criteria for osteopenia/osteoporosis who were randomized to switch from tenofovir to abacavir (n=26) or to continue with tenofovir (n=28). Forty-eight weeks after switching to abacavir, hip BMD improved by 2.1% (95% CI, −0.6, 4.7) (p=0.043). Now we present changes from baseline to week 48 in bone markers in 44 of these patients: 1) C-terminal telopeptide of collagen type 1 (CTX) (resorption), and 2) osteocalcin (OCN) and procollagen type 1 N propeptide (P1NP) (bone formation). Additionally, we assessed changes in circulating levels of 3 proteins involved in bone regulation: osteoprotegerin (OPG), receptor activator for nuclear factor K B ligand (RANKL) and sclerostin (SOST), a selective regulator of bone formation through the Wnt pathway, no previously explored in this population. To compare between study groups, chi-Squared or Fisher and Student t tests were performed according to each variable distribution.

Results: CTX, OCN and P1NP significantly decreased only in the abacavir group [mean (SD) CTX, from 0.543 (0.495) to 0.301 (0.306) ng/mL (p<0.001); OCN, from 23.72 (22.20) to 13.95 (12.40) ng/mL (p=0.209); P1PN, from 54.68 (54.52) to 28.65 (27.48) ng/mL (p<0.001)], reaching significant differences between groups at week 48. Osteoprotegerin did not vary in any group but SOST significantly increased in the abacavir group (from 29.53 (27.91) to 35.56 (34.59) pmol/L, p=0.002). No significant differences in OPG and SOST were detected between groups at week 48. RANKL values were below the limit of detection in all samples assessed.

Conclusions: The switch from tenofovir to abacavir seems to induce a positive effect on bone tissue since bone remodelling decreased and circulating sclerostin levels increased, both associated with better bone properties (density, microarchitecture and strength), and decreased risk of fracture.

768 Relationship Between Phosphate Reabsorption, Age, Tenofovir and Bone Mineral Density

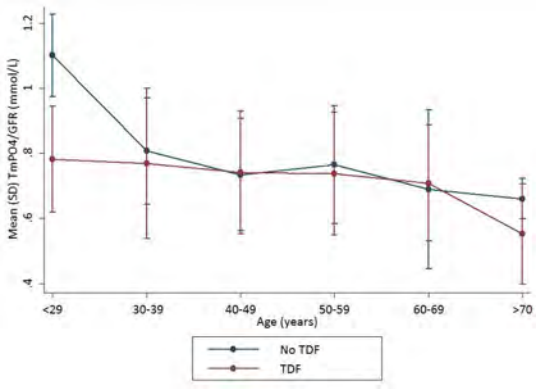
Lisa Hamzah[2]; **Amanda Samarawickrama**[1]; Karen Walker-Bone[3]; Yvonne Gilleece[4]; Martin Fisher[1]; Frank A. Post[5]

[1]Brighton and Sussex Medical School, London, United Kingdom; [2]King's College London, London, United Kingdom; [3]University of Southampton, Southampton, United Kingdom; [4]Brighton and Sussex Hospitals NHS Trust, Brighton, United Kingdom; [5]King's College Hospital NHS Foundation Trust, London, United Kingdom

Background: The functional capacity of renal tubules to reabsorb phosphate declines with age. The extent to which this is affected by tenofovir (TDF) exposure and its effects on bone are unknown. We investigated the association between phosphate reabsorption, age, TDF exposure and bone mineral density (BMD).

Methods: Male HIV-positive patients taking part in a prospective study to evaluate BMD were analysed for phosphate wasting using maximum threshold for phosphate reabsorption ($TmPO_4$/GFR), derived by the Kenny and Glen algorithm. Bone resorption was assessed by serum carboxy-terminal collagen crosslinks (CTX), bone formation by type 1 procollagen (P1NP), and BMD by dual-energy x-ray absorptiometry. Correlation coefficients and linear regression were used to evaluate relationships between variables.

Results: 411 men (mean age 47.4 [SD 9.8] years, 94.3% white, 92.9% MSM, diagnosed for a median 9.6 [IQR 5.0-15.5] years, 69.4% on TDF) were included. $TmPO_4$/GFR correlated with age (r^2=-0.2, p=0.006), parathyroid hormone (PTH) concentrations (r^2=0.1, p=0.02) and, in those over 50 years, with lumbar spine BMD (r^2=-0.2, p=0.02). Among subjects aged 30-70 years on antiretroviral therapy, $TmPO_4$/GFR did not differ among those exposed versus those not exposed to TDF (Figure). In multivariable analysis, $TmPO_4$/GFR remained associated with older age (β -0.03 [95% CI -0.05, -0.01] per 10 years, p=0.003) and 25 (OH) vitamin D (β 0.001 [95% CI 0.0001, 0.002] p=0.03), while univariable associations with nadir CD4 cell count, prior AIDS, HIV viral load, TDF and protease inhibitor exposure, P1NP and PTH were no longer significant after adjustment. $TmPO_4$/GFR was not associated with CTX (p=0.9), BMD spine (p=0.1), BMD total hip (p=0.5) or BMD femoral neck (p=0.5).



Mean maximum threshold for phosphate reabsorption ($TmPO_4$/GFR) according to tenofovir (TDF) exposure, stratified by age

Conclusions: In HIV-positive men, reduced phosphate reabsorption was common. Similar to observations reported in the general population, $TmPO_4$/GFR declined with age but was not significantly associated with TDF exposure, increased bone resorption, or lower BMD. Our results suggest that in patients stable on antiretroviral therapy, $TmPO_4$/GFR may not be useful in identifying patients at increased risk of bone loss.

769LB Less Bone Loss With a Maraviroc Regimen in HIV-Infected Treatment-Naïve Subjects

Babafemi Taiwo[1]; Ellen Chan[2]; Carl Fichtenbaum[3]; Heather Ribaudo[2]; Athe Tsibris[4]; Karin Klingman[5]; Joseph J. Eron[6]; Baiba Berzins[1]; Todd T. Brown[7]
ACTG A5303 Study Team

[1]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [2]Statistical and Data Analysis Center, Harvard School of Public Health, Boston, MA, US; [3]University of Cincinnati, Cincinnati, OH, US; [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [5]National Institutes of Health, Bethesda, MD, US; [6]University of North Carolina at Chapel Hill, Chapel Hill, NC, US; [7]Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: Bone mineral density (BMD) decreases by 2-6% in the first 2 years of antiretroviral therapy (ART). The decline is 1-2% greater with tenofovir (TDF) than other nucleos(t)ide reverse transcriptase inhibitors (NRTI). The effects of maraviroc (MVC) on BMD are unknown. We investigated a novel regimen containing MVC dosed 150mg once daily (QD).

Methods: A 48 wk double-blind, placebo-controlled trial was conducted at US ACTG and ATN sites. Subjects were HIV-1-infected, ART-naïve with viral load (VL) >1000 c/mL and R5 tropism on Trofile®. Exclusion criteria included any major NRTI or darunavir (DRV) mutation; active hepatitis B; and CrCl <50 mL/min. Subjects were randomized 1:1 to MVC 150mg or TDF 300mg QD, stratified by VL< and ≥100,000 c/mL and age < and ≥30 yrs. All subjects received DRV 800mg, ritonavir (RTV) 100mg, and emtricitabine (FTC) 200mg QD. Dual-energy x-ray absorptiometry (DXA) scanning was done at baseline and wk48. Primary endpoint was percentage change in total hip BMD from baseline to wk48. Secondary endpoints included percentage change in lumbar spine BMD, time to virologic failure (VF), and change in CD4 count. VF was defined as confirmed VL >1000 c/mL at or after wk16 and before wk24, or confirmed VL > 200 c/mL at or after wk24. All analyses were as-treated. P-values were not adjusted for multiple comparisons

Results: We enrolled 262 subjects. The analysis population (N=259; 130 MVC, 129 TDF) was 91% male; median age 33yrs, 45%White, 30%Black, 22%Hispanic. At baseline, median VL was 4.5 $\log_{10}$ c/mL and CD4 count was 390 cells/mm^3. Decline in hip BMD (as-treated N=115 for MVC, 109 for TDF) from baseline to wk48 was less with MVC: median (Q1, Q3) change in BMD of -1.51% (-2.93%, -0.11%) vs -2.40% (-4.30%, -1.32%) for TDF (Wilcoxon p<0.001). Median lumbar spine BMD decline was also less with MVC (-0.88% vs -2.35%, p<0.001). Virologic outcomes in both arms were good; VF probabilities by wk24 were 4% for MVC vs. 2% for TDF, and 6% vs. 5% by wk48 (log-rank p=0.57). VL ≤50 c/mL was 85%MVC vs. 93%TDF at wk24 (p=0.06) and 94% in each arm at wk48 (p=0.89). CD4 change from baseline to wk48 was greater with MVC; median of +234 vs. +188 cells/mm^3, p=0.036. At wk48, CrCl was >90 mL/min in 90%MVC, 91%TDF. All results were similar with ITT analyses. Both regimens were well-tolerated

Conclusions: Initiating ART with QD MVC, FTC and DRV/RTV resulted in less bone loss compared to TDF-based therapy with no apparent difference in virologic efficacy. MVC may be an option to attenuate early bone-loss

TUESDAY, FEBRUARY 24, 2015

Session P-Q3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Bone Disease: Mechanisms of Bone Loss and Fracture Risk

770 Association of Adipokines With Bone Mineral Density in HIV+ and HIV- Women

Anjali Sharma[1]; Yifei Ma[2]; Rebecca Scherzer[2]; Amber L. Wheeler[2]; Mardge Cohen[3]; Deborah Gustafson[4]; Michael T Yin[5]; Phyllis C. Tien[2]

[1]Albert Einstein College of Medicine, Bronx, NY, US; [2]University of California San Francisco, San Francisco, CA, US; [3]John H. Stroger Jr. Hospital of Cook County, Chicago, IL, US; [4]State University of New York Downstate Medical Center, Brooklyn, NY, US; [5]College of Physicians and Surgeons, Columbia University, New York, NY, US

Background: HIV infection is associated with low bone mineral density (BMD) and alterations in adipose-derived hormones (adipokines) such as leptin and adiponectin. Studies in the general population suggest that adipokines may be important mediators of the relationship between fat and bone, however their relationship to BMD in HIV+ populations is unknown.

Methods: BMD of the lumbar spine (LS), total hip (TH), and femoral neck (FN) were measured by dual X-ray absorptiometry (DXA) at baseline and over 5 years in 440 participants (318 HIV+, 122 HIV-) enrolled in the Metabolic Substudy of the Women's Interagency HIV Study. Serum leptin and adiponectin were assayed on stored sera. Multivariable linear mixed models were used to assess the effects of adipokines and HIV status on BMD over 5 years, adjusting for demographic, behavioral, and body composition and metabolic factors, and menopausal status. Models restricted to HIV+ women also adjusted for CD4, HIV RNA, and HAART use.

Results: Compared with HIV- women, HIV+ women were older (mean 44 vs. 37 years) and more likely to be post-menopausal (26% vs. 3%). HIV+ women had lower BMI (27kg/m^2 vs. 30kg/m^2), and lower leptin (18ng/mL vs. 28ng/mL) but higher adiponectin (9.4μg/mL vs. 6.4μg/mL) levels at the baseline visit. In unadjusted analysis, HIV+ women had lower

LS, TH, and FN BMD than HIV- women. After adjustment for demographic, behavioral, body composition and metabolic factors, HIV+ status was associated with lower BMD at the TH, (-0.047 g/cm^2), FN (-0.048 g/cm^2), and LS (-0.077 g/cm^2) (all p<.05). There was little change in the effects of HIV on BMD after additional adjustment for adiponectin levels; HIV remained associated with lower BMD at the TH (-0.045 g/cm^2), FN (-0.048 g/cm^2) and LS (-0.078 g/cm^2) (all results p<0.01). Similar findings were observed after additional adjustment for leptin. Among HIV+ women, in unadjusted analyses, adiponectin was associated with lower TH BMD (-0.025 g/cm^2 per 10-fold adiponectin increase, p=0.04), whereas leptin was associated with *higher* BMD at FN (+0.027 g/cm^2 per 10-fold leptin increase, p=0.005) and TH (+0.019 g/cm^2, p=0.03). After multivariable adjustment, neither adiponectin nor leptin were associated with BMD at any site (all p>0.10).

Conclusions: HIV infection is associated with lower TH, FN, and LS BMD among women. Serum leptin and adiponectin levels do not appear to mediate the association of HIV infection with loss of BMD, and appear to have little association with BMD among HIV infected women.

771 Long-Term Changes in Bone Mineral Density and Insulin Resistance on Statins in HIV

Kristine M. Erlandson[1]; Ying Jiang[2]; Sara M. Debanne[2]; Grace A. McComsey[2]

[1]University of Colorado, Aurora, CO, US; [2]Case Western Reserve University, Cleveland, OH, US

Background: We previously demonstrated increased hip bone mineral density (BMD) and worsening in insulin resistance after 48 weeks of rosuvastatin in HIV-infected adults on antiretroviral therapy (ART). Here, we present the final 96 week results.

Methods: The Stopping Atherosclerosis and Treating Unhealthy bone with RosuvastatiN in HIV (SATURN-HIV) trial is a randomized, double-blind, placebo-controlled trial to evaluate the effect of rosuvastatin on markers of cardiovascular risk and skeletal health in HIV over 96 weeks. Subjects were on stable ART with HIV-1 RNA <1000 copies/mL, LDL-cholesterol <130 mg/dL, and immune activation (CD8+CD38+HLA-DR+ >19% and/or hsCRP >2 mg/L). Subjects were randomized 1:1 to daily rosuvastatin 10 mg or matching placebo, and stratified by protease inhibitor use and presence/absence of osteopenia. Bone primary endpoint was DXA-measured changes in total hip BMD; secondary endpoint was change in homeostatic model assessment of insulin resistance (HOMA-IR), calculated as fasting [insulin (uIU/mL)*glucose (mg/dL)]/450. Primary analyses were intent-to-treat. Statistical tests included multivariable linear regression.

Results: 147 subjects enrolled;78% male, 70% black; median age 47 years and CD4 count 613 cells/μL; 78% had HIV-1 RNA<50 copies/mL. At baseline, study arms were well balanced; 23% were osteopenic at the hip and 22% at the spine. No participants had diabetes, but 18% in statin and 15% in placebo had fasting glucose >100 mg/dL. At week 96, no significant differences in hip BMD (p=0.52) or spine BMD (p=0.96) were seen between study arms. Although changes in fasting glucose by week 96 were not significantly different between the rosuvastatin and placebo (p=0.14), 20 (32%) in the rosuvastatin and 12 (5%) in the placebo arm had glucose >100 mg/dL and 1 (2%) in the rosuvastatin and 2 (3%) in the placebo arm had fasting glucose >125 mg/dL. The rosuvastatin arm had significantly greater 96 week increases in insulin (mean 49.8 [SE 86.4]% versus 20.2 [138.4]%; p=0.009) and in HOMA-IR (72.6 [109.9]% vs. 33.0 [158.3]%; p=0.009). In multivariate models, 96 week changes in HOMA-IR were associated with statin use but not age, race, family history of diabetes, hepatitis C, or change in body composition.

Conclusions: Despite an initial beneficial effect of rosuvastatin on hip BMD, no longer term benefit was observed. The detrimental impact on insulin resistance persisted. Further data is needed to determine the risk/benefit of statins in HIV-infected persons.

772 Immunologic Predictors of Bone Loss in a Contemporary HIV Cohort

Edgar T. Overton[1]; Katherine H. Hullsiek[2]; Gerome Escota[3]; Kenneth A. Lichtenstein[4]; Lois Conley[5]; Pragna Patel[5]; John T. Brooks[5]; Irini Sereti[6]; Jason V. Baker[2]
the CDC SUN (Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy) Investigators

[1]University of Alabama at Birmingham, Birmingham, AL, US; [2]University of Minnesota, Minneapolis, MN, US; [3]Washington University School of Medicine, St. Louis, MO, US; [4]National Jewish Health, Denver, CO, US; [5]Division of HIV/AIDS Prevention, Atlanta, GA, US; [6]National Institute of Allergy and Infectious Disease (NIAID), Bethesda, MD, US

Background: HIV is a recognized risk factor for osteoporosis. The role of soluble markers and cellular immune parameters on HIV-related bone loss remains unclear.

Methods: We evaluated inflammatory markers and total hip bone mineral density (BMD) changes in a prospective HIV cohort enrolled during 2004-2006 (SUN Study). We abstracted clinical data & measured BMD by dual-energy X-ray absorptiometry (DXA) at baseline & annually for 4 years. We characterized soluble inflammatory biomarkers & cellular immunophenotypes by multi-color ow cytometry of baseline cryopreserved peripheral blood mononuclear cells, assessed the correlation between baseline BMD & immune parameters, and identified predictors of percent change in BMD from baseline by longitudinal regression after adjusting for traditional & HIV-related risk factors.

Results: Baseline characteristics (n=637): median age 41 yrs, 77% male, median CD4 ct 471c/mm^3, and 74% plasma HIV RNA level <400 cp/mL. There were 554 subjects with 1887 yrs of follow up (median 4 yrs) and a median of 4 DXAs per participant. At baseline and final DXA, 387 (61%) and 393 (62%) had low BMD (T score <-1.0), respectively. sCD14, but not IL-6, was inversely correlated with total hip BMD at baseline (p<0.01 & 0.08, respectively). No T-cell phenotypes correlated with baseline hip BMD while several monocyte phenotypes correlated either positively (CX3CR1+; CD14^{dim}CD16+; CD14^{var}CD16+) or negatively (CCR2+; CD14+CD16-) with baseline hip BMD (p<0.01 for all). Associations between baseline soluble biomarkers and frequencies of immunophenotypes with changes in total hip BMD were adjusted for traditional (model 1) and HIV-related risk factors (model 2) (see table). Having a higher prevalence of memory CD28+ CD4+ and CD8+ T-cells was associated with increasing total hip BMD (p<0.001 for both). IL-6, replicatively senescent CD4 T-cells, and monocytes expressing CCR5+ or tissue factor were associated with total hip BMD decline (p=0.01, 0.03, & 0.05, respectively). For T-cell activation phenotypes and other monocyte phenotypes, no apparent association with change in total hip BMD was identified.

Table: Immunologic predictors of total hip BMD change in the SUN Study (n=554)

Soluble Biomarker	Model 1* Regression coefficient# (95% CI)	p-value	Model 2* Regression coefficient# (95% CI)	p-value
IL-6 (pg/mL)	-0.61 (-1.00, -0.23)	<0.01	-0.43 (-0.85, 0.00)	0.05
sCD14 (g/mL)	-0.77 (-1.72, 0.18)	0.11	-0.44 (-1.43, 0.54)	0.38
sCD163 (pg/L)	-0.34 (-0.76, 0.07)	0.10	-0.22 (-0.65, 0.22)	0.33
Monocyte Phenotypes				
CD14+/CD16+	-0.20 (-0.60, 0.21)	0.34	-0.13 (-0.55, 0.29)	0.55
CD14^{dim}/CD16+	-0.02 (-0.37, 0.33)	0.91	-0.13 (-0.48, 0.23)	0.48
CCR2+	0.23 (-2.62, 3.08)	0.88	0.51 (-2.40, 3.42)	0.73
CCR5+	-0.22 (-0.47, 0.02)	0.07	-0.27 (-0.51, -0.02)	0.03
Tissue Factor (TF)+	-0.27 (-0.56, 0.02)	0.07	-0.29 (-0.58, -0.01)	0.05
T-Cell Phenotypes				
CD4+/HLADR+/CD38+	-0.19 (-0.51, 0.13)	0.25	0.00 (-0.33, 0.33)	0.99
CD4+/CD57+/CD38+	-0.23 (-0.50, 0.04)	0.09	-0.34 (-0.61, -0.07)	0.01
Memory CD4+/CD28+	0.76 (0.28, 1.23)	<0.01	0.79 (0.34, 1.25)	<0.001
CD8+/HLADR+/CD38+	-0.00 (-0.35, 0.34)	0.98	0.24 (-0.12, 0.60)	0.18
CD8+/CD57+/CD38+	-0.11 (-0.50, 0.28)	0.57	-0.01 (-0.41, 0.40)	0.98
Memory CD8+/CD28+	0.74 (0.40, 1.09)	<0.001	0.71 (0.35, 1.06)	<0.001

**Model 1 is adjusted for age, gender, race, smoking, hepatitis B or C co-infection, and cholesterol and blood pressure treatment, and prior AIDS diagnosis. Model 2 additionally adjusted for CD4, HIV VL and time on ART.*
#Regression coefficient represents an absolute percent change from baseline BMD per doubling of given biomarker or cellular phenotype.

Conclusions: In this healthy HIV adult cohort with predominantly controlled viremia, total hip BMD decline was associated with IL-6, replicative senescent T-cells, CCR5+ and tissue factor expressing monocytes. Memory CD4+ and CD8+ CD28+ T cells were associated with increases in BMD. Immunologic alterations that persist after virologic suppression may contribute to ongoing loss of BMD.

773 RANKL Predicts 96-Week BMD Changes in ATV/r Monotherapy: A MODAt Trial Sub-Study

Vincenzo Spagnuolo[1]; Marco Borderi[2]; Giuseppina Musumeci[2]; Laura Galli[1]; Camilla Tincati[3]; Stefano Rusconi[3]; Giovanni Guaraldi[4]; Alba Bigoloni[1]; Adriano Lazzarin[1]; Antonella Castagna[1]

[1]San Raffaele Scientific Institute, Milan, Italy; [2]Alma Mater Studiorum University of Bologna, Bologna, Italy; [3]University of Milan, Milan, Italy; [4]University of Modena and Reggio Emilia, Modena, Italy

Background: To evaluate the association between bone biomarkers and changes in bone mineral density (BMD) over 96 weeks in patients treated with atazanavir/ritonavir (ATV/r) monotherapy vs ATV/r+2 N(t)RTIs.

Methods: MODAt (NCT01511809) is a multicentric, randomized, open-label, non-inferiority trial. Patients on ATV/r 300/100mg+2 N(t)RTIs since≥48 weeks, virologically suppressed since≥24 weeks, randomized to ATV/r monotherapy (arm A) or to maintain ATV/r+2N(t)RTIs (Arm B). This sub-study included patients who maintained for 96 weeks the antiretroviral treatment assigned at randomization.

Participants underwent DXA scan and tested bone biomarkers at baseline (BL), week 48, week 96/discontinuation.

Results as median (IQR). Linear regression to evaluate the predictors of 96-week percent changes in vertebral and femoral (total proximal) BMD.

Results: 69 patients [29 patients on ATV/r monotherapy, 40 patients on ATV/r+2N(t)RTIs], age 42 (35-46) years, 84% males, 58% smokers, 17% HCV co-infected, BMI 23.6 (21.6-25.6) kg/m^2, BL CD4+ 599 (432-744) cells/μL, 87% on TDF at randomization.

At lumbar spine, BL BMD was 0.975 (0.920 ; 1.047) g/cm^2 and 1.016 (0.933; 1.103) g/cm^2 in arm A and B, respectively (p=0.359); %change from BL to week 48 were 1.772 (-0.010; 3.998) and -0.988 (-2.270; 1.143) in arm A and B, respectively (p=0.002) while %change from BL to week 96 were 0.830 (-0.299; 2.388) and -0.811 (-3.207; 1.833) in arm A and B, respectively (p=0.075).

At total proximal femur, BL BMD was 0.929 (0.874; 0.973) g/cm^2 and 0.959 (0.871; 1.024) g/cm^2 in arm A and B, respectively (p=0.458); %change from BL to week 48 were 1.301 (0.020; 3.912) and -0.199 (-1.835; 1.738) in arm A and B, respectively (p=0.069) while %change from BL to week 96 were 1.321 (-0.649; 2.671) and -0.471 (-2.440; 1.209) in arm A and B, respectively (p=0.071).

BL values of bone biomarkers were similar in the two arms [Arm A: osteocalcin, 20.4 (14.2; 29.5) ng/ml; CTX-I, 0.63 (0.44; 0.82) ng/ml; vitamin D, 62 (52; 113) nmol/L; OPG, 988 (707; 1395) pg/ml; RANKL, 31 (31; 61) pg/ml; Arm B: osteocalcin, 25.2 (15.9; 33.3) ng/ml (p=0.342); CTX-I, 0.48 (0.35; 0.69) ng/ml (p=0.095); vitamin D, 99 (59; 142) nmol/L (p=0.167); OPG, 1046 (726; 1418) pg/ml (p=0.985); RANKL, 31 (31; 42)pg/ml (p=0.685)]. Results from multivariate analysis in Table 1.

Table1 – Multivariate linear regression analysis: adjusted means of % change in BMD at week 48 and at week 96 according to study treatment and BL RANKL.

	Lumbar Spine L1-L4 BMD				Total proximal femur BMD			
	Adjusted § means of % 48-week change in BMD [standard error]	p-value	Adjusted § means of % 96-week change in BMD [standard error]	p-value	Adjusted § means of % 48-week change in BMD [standard error]	p-value	Adjusted § means of % 96-week change in BMD [standard error]	p-value
Study arm		0.252		0.759		0.025		0.012
ATV/r monoteraphy	0.38 (1.22)		-0.94 (1.41)		1.44 (0.83)		1.16 (1.01)	
ATV/r + 2N(t)RTIs	-1.11 (1.31)		-1.40 (1.52)		-0.58 (0.88)		-1.64 (1.07)	
Baseline RANKL		0.026		0.167		0.011		0.128
<32 pg/ml	1.21 (1.17)		-0.07 (1.36)		1.62 (0.79)		0.59 (0.96)	
≥32 pg/ml	-1.93 (1.39)		-2.27 (1.61)		-0.76 (0.92)		-1.08 (1.12)	
ATV/r monoteraphy and BL RANKL <32 pg/ml	2.78 (1.36)	0.013	0.64 (1.57)	0.201	2.44 (0.92)	0.001	1.23 (1.12)	0.003
ATV/r monoteraphy and BL RANKL ≥32 pg/ml	-2.01 (1.79)	0.941	-2.52 (2.07)	0.858	0.44 (1.21)	0.120	1.09 (1.47)	0.024
ATV/r + 2N(t)RTIs and BL RANKL <32 pg/ml	-0.37 (1.32)	0.394	-0.77 (1.53)	0.531	0.80 (0.89)	0.018	-0.04 (1.08)	0.024
ATV/r + 2N(t)RTIs and BL RANKL ≥32 pg/ml	-1.85 (1.78)	Ref	-2.03 (2.06)	Ref	-1.96 (1.17)	Ref	-3.24 (1.43)	Ref

§ adjusted for age, gender, body mass index, smoking, HCV, baseline CD4+, vitamin D or calcium supplementation, BL osteocalcin, BL CTX-I, BL vitamin D, BL osteoprotegerin.

Conclusions: At 96-week of ATV/r monotherapy, this strategy was associated with an increase in BMD; the benefit of ATV/r monotherapy was more evident in patients with low baseline values of RANKL.

774 Predictors of Longitudinal Change in Bone Mineral Density in a Cohort of HIV Positive and Negative Subjects

Willard Tinago[1]; Aoife Cotter[1]; Caroline Sabin[2]; Alan Macken[1]; Eoin Kavanagh[3]; Jennifer Brady[4]; Geraldine McCarthy[5]; Juliet Compston[6]; Patrick W. Mallon[1]
HIV UPBEAT Study Group

[1]University College Dublin, Dublin, Ireland; [2]Research Department of Infection and Poulation Health, London, United Kingdom; [3]Mater Misericordiae University Hospital, Dublin, Ireland; [4]Mater Misericordiae University Hospital, Dublin, Ireland; [5]Mater Misericordiae University Hospital, Dublin, Ireland; [6]University of Cambridge, London, United Kingdom

Background: Although HIV infection is associated with low bone mineral density (BMD) in cross-sectional studies, whether it is associated with greater declines in BMD over time remains unclear. We aimed to compare rates of, and factors associated with, change in BMD over time between HIV-positive and -negative subjects, and to determine HIV-related predictors of change in BMD.

Methods: A prospective, 3-year, cohort enrolled HIV positive and negative subjects; demographic, clinical, and medication data were collected, with annual dual xray absorptiometry (DXA) at femoral neck (FN), total hip (TH) and lumbar spine (LS) and fasting bloods, including alkaline phosphatase (ALP) and bone biomarkers (C-terminal cross-linking telopeptide of type-1 collagen (CTX-1), procollagen type-1 amino-terminal propeptide (P1NP), osteocalcin (OC). Of the 384 subjects (176 (45.8%) HIV positive),120 subjects contributed two and 264 contributed 3 BDM annual measurements. Longitudinal mixed models were used to compare and determine predictors of rate of absolute change in BMD in the whole cohort and within the HIV sub-group.

Results: Compared to HIV negative group, those with HIV were younger, more likely to be male and less likely to be Caucasian. Those with HIV had lower baseline BMD at FN, TH and LS (all p<0.05, Table 1). Although BMD declined at all three sites in both groups (Table 1), there was no signficant between-group difference in rate of absolute change in BMD at LS (+0.002 g/cm^2/year, p=0.51), TH (-0.001 g/cm^2/year, p=0.69) and FN (-0.004 g/cm^2/year, p=0.08) after adjustment for age, gender, ethnicity, smoking status and body mass index.

In a HIV-specific sub-analyses (table 1), one IU/L increase in baseline ALP was independently associated with a greater subsequent BMD loss at FN (0.00016 g/cm^2/year loss, p=0.016). Additional adjustment for CTX-1, P1NP or OC did not change this association and longitudinal changes in BMD were not associated with current or cumulative exposure to tenofovir disoproxil fumarate (TDF), nadir CD4+T-cell count, or traditional risk factors of age, gender, ethnicity, PTH and 25(OH) D.

Characteristics of HIV-positive and HIV negative participants

	HIV pos (176)	HIV neg (208)	P		HIV pos	HIV neg	P
Age (years)	39 (34-46)	43 (35-50)	0.039	FN BMD - BL (g/cm2)	1.024 (0.927,1.135)	1.055 (0.964,1.159)	0.0025
% male	61%	46%	0.003	Change (g/cm2/yr)	-0.0063	-0.003	0.08
% Caucasian	58%	80%	<0.001		(-0.01, -0.003)	(-0.005, -0.0004)	
% Heterosexual, MSM, IDU	51%, 31%, 17%			TH BD - BL (g/cm2)	1.061 (0.942, 1.157)	1.107 (1.00,1.196)	0.003
Years since HIV diagnosis	4.0 (2.0-9.0)			- Change (g/cm2/yr)	-0.0044	-0.0036	0.69
Currently on ART	155 (88%)				(-0.007, -0.002)	(-0.006, -0.0012)	
ART exposure (years)	2.9 (0.7-5.4)			LS BMD - BL g/cm2)	1.164 (1.061,1.304)	1.238(1.135,1.348)	0.001
% on TDF	83%			- Change (g/cm2/yr)	-0.0024	-0.0041	0.51
exposure (years)	1.3 (0.1-2.9)				(-0.007, 0.002)	(-0.008, 0.0005)	
Nadir CD4+ (cells/mm3)	218 (134-309)						
Current CD4+ (cells/mm3)	508 (370-650)						

Data are median (IQR) unless specified. ART = antiretroviral therapy, MSM = men who have sex with men. IDU = intravenous drug user. TDF = tenofovir disoproxil fumarate. BMD = bone mineral density. TH = total hip. FN = femoral neck. LS = lumbar spine. BL = baseline.

Conclusions: Although those with HIV have lower BMD, we observed no difference in rate of BMD loss between groups over time. That higher ALP was associated with greater decreases in FN BMD in those with HIV may reflect altered bone turnover, although exposure to TDF was not implicated in progressive BMD loss.

775 Fracture Incidence Is Increased in Aging HIV-Infected Women

Anjali Sharma[1]; Qiuhu Shi[2]; Donald R. Hoover[3]; Kathryn Anastos[1]; Phyllis C. Tien[4]; Mary A. Young[5]; Mardge Cohen[6]; Deborah Gustafson[7]; Michael T Yin[8]

[1]Albert Einstein College of Medicine, Bronx, NY, US; [2]New York Medical College, Valhalla, NY, US; [3]Rutgers University, Piscataway, NJ, US; [4]University of California San Francisco, San Francisco, CA, US; [5]Georgetown University, Washington D.C., DC, US; [6]John H. Stroger Jr. Hospital of Cook County, Chicago, IL, US; [7]State University of New York Downstate Medical Center, Brooklyn, NY, US; [8]College of Physicians and Surgeons, Columbia University, New York, NY, US

Background: Low bone mineral density (BMD) is common among HIV-infected individuals. Some studies find higher fracture incidence in HIV+ than HIV- individuals. There is particular concern for increased rates of fracture in older HIV-infected women as they continue to age.

Methods: We analyzed a cohort of 2375 (1713 HIV+, 662 HIV-) women enrolled in the Women's Interagency HIV Study (WIHS) to evaluate the effects of HIV infection on time to first self-reported fragility and non-fragility fracture, and determine risks for incident fracture, between 2003-2013. Incident fractures were assessed at semiannual visits. Associations of traditional fracture risk factors and HIV disease characteristics measured at index visit with subsequent incident fracture were estimated using proportional hazards models.

Results: HIV+ women were older than HIV- (median 40 vs 35 yrs) and had lower body mass index (28 vs 30kg/m^2), but were racially similar (59% vs 62% black). HIV+ women were more likely to be post-menopausal (19% vs 11%), HCV infected at study entry (24% vs 15%), and use vitamin D at index visit (42% vs 28%), but less likely to smoke (45% vs 51%). Among HIV+, mean CD4+ count was 480 cells/μL and 63% were taking HAART at index visit. New fractures occurred in 300 (17.5%) HIV+ women and 90 (13.6%) HIV- women, including new fragility fractures in 82 (4.8%) HIV+ and 24 (3.6%) HIV- women. Unadjusted fracture incidence rates were higher in HIV+ versus HIV- women (2.19 vs 1.54/100py, p=0.002); however, unadjusted incidence rates of fragility fractures did not statistically differ (0.56/100py vs. 0.39/100py, p=0.13). Adjusted for age, race, prior fracture, and history of cocaine and injection drug use, HIV+ women had significantly higher incidence rate of any fracture compared with HIV- women (aHR1.30; 95% CI 1.02-1.66). Among HIV+ women, older age, white race, prior fracture, smoking, and prior AIDS defining illness (aHR=1.56; 95% CI: 1.22-1.98) significantly predicted new fracture, while CD4+ count and antiretroviral exposure did not.

Conclusions: Fracture rates were higher among HIV+ than HIV- women. Cocaine and injection drug use were also significant predictors of incident fracture. Further research is needed to understand whether the risk of fracture associated with cocaine use relates to increased rate of falls, or direct effects on bone metabolism. Our data support optimizing musculoskeletal health in older HIV-infected women.

TUESDAY, FEBRUARY 24, 2015

Session P-Q4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Measuring Bone Density

776 Heel Quantitative Ultrasound to Cut Down on DXA Costs in HIV-infected Patients

Marilia R. Pinzone; Maria Gussio; Daniela Castronuovo; Adriana Di Gregorio; Benedetto M. Celesia; Bruno Cacopardo; Giuseppe Nunnari

University of Catania, Catania, Italy

Background: HIV infection has been associated with increased risk of osteopenia/osteoporosis and fragility fractures. DXA is the reference standard to assess bone mass density (BMD), however it is a radiation-based and expensive technique, not easily accessible in several clinical settings. Quantitative ultrasound (QUS) of the heel is a radiation-free, easy-to-perform technique, which may help reducing the need for DXA scan.

Methods: In this cross-sectional study, we evaluated the prevalence of and risk factors for low BMD by QUS (Hologic Sahara) in a cohort of HIV-infected patients. We assessed the correlation between BMD and demographic, viro-immunological and biochemical parameters. Osteopenia/osteoporosis rates were compared with those of 36 sex- and age-matched HIV-negative controls. Mann-Whitney test was used to compare continuous variables, Chi-squared test for categorical variables. Spearman's correlation and multivariate analysis were used to assess factors associated with low BMD.

Results: 152 HIV-positive patients were enrolled, 29% female, median age 47(IQR 39-54) years. 19% of patients were HCV-positive, 60% smokers, 7% had diabetes. Median BMI was 24(IQR 22-26) kg/m^2. Median time since HIV diagnosis was 122(IQR 47-216) months, median time from HAART initiation 119(IQR 39-204) months. 91% were on HAART, 53% were receiving a PI-based regimen, 44% a NNRTI-based one, 11% were taking RAL, 60% TDF, 80% had undetectable viral load, median CD4 count was 548 (IQR 407-695) cells/μl.

The number of subjects with Sahara t-score <-1 was significantly higher among HIV-positive patients in comparison with controls (64 *vs.* 33%, p=0.012). 55% of HIV-positive patients had Sahara t-score <-1, 9% <-2.5). In the univariate but not in the multivariate analysis, factors associated with lower BMD were older age (p=0.002), lower CD4 at diagnosis (r=0.35, p=0.003), duration of tenofovir exposure (r=-0.19, p=0.02) and HCV coinfection (p=0.01).

According to guidelines, 41% of patients had risk factors for osteoporosis who make them eligible for DXA. By using QUS, we may avoid/delay DXA in around 30% of them. On the other hand, 59% of patients ineligible for DXA according to US HIV guidelines, had a low QUS t-score.

Conclusions: In our cohort, low BMD was highly prevalent. Heel QUS is a quick, easy-to-perform, relatively inexpensive and radiation-free technique which may help reducing the need for unnecessary DXA as well as identifying high-risk subjects, requiring a thorough workup.

777 Novel Radiographic Measures HRpQCT and HSA as Correlates of HIV-Associated Fractures

Darrell H. Tan[1]; Janet Raboud[2]; Leah Szadkowski[2]; Eva Szabo[4]; Hanxian Hu[4]; Queenie Wong[4]; Angela Cheung[4]; Sharon Walmsley[3]

[1]St. Michael's Hospital, Toronto, Canada; [2]Toronto General Research Institute, Toronto, Canada; [3]University Health Network, Toronto, Canada; [4]Centre for Excellence in Skeletal Health Assessment, Toronto, Canada

Background: Bone mineral density as assessed by dual energy x-ray absorptiometry (DXA) is often used to assess fracture risk, but is limited by the lack of a clear fracture threshold and of validation in HIV. We conducted a pilot case-control study to determine whether novel radiologic methods such as total volumetric BMD (tvBMD) at the distal radius by high resolution peripheral quantitative computed tomography (HRpQCT) and buckling ratio (BR) at the narrow neck by hip structural assessment (HSA) correlate with fracture in HIV patients.

Methods: Adults with a history of low-trauma fractures after their HIV diagnosis (cases) were matched 1:1 with HIV-infected adults with no prior fractures (controls) based on age, sex, race and smoking history. Participants underwent DXA, HRpQCT and HSA once. Conditional logistic regression was used to model the relationship between fracture and DXA-derived T-scores, adjusting for the duration of HIV infection at the time of the fracture. After further adjustment for each novel radiologic parameter, nested models were compared using the likelihood ratio (LR) test to determine whether any offered additional information independent of DXA.

Results: 23 matched pairs were included. Median (interquartile range, IQR) age was 50 (46,56) years, 78% were male, 78% were white and 57% were smokers. Median (IQR) duration of HIV at the time of bone measurements was 19 (11,23) years for cases and 10 (7,18) years for controls; nadir CD4 was 234 (123,370) and 166 (36,410) cells/mm^3 respectively. 4 cases and 0 controls had ever used osteoporosis medications. DXA-derived T-scores showed trends towards association with fracture, with OR=0.87 per SD of T-score (95%CI=0.53,1.43) for the L-spine and OR=0.43 (95%CI=0.17,1.12) for the hip. When tvBMD was included in the hip model, the tvBMD estimate was not significant (OR=1.29 per 10mg/cm^3, 95%CI=0.93,1.81), but the strength of the DXA-derived T-score increased (OR=0.11, 95%CI=0.01,1.08) as did model fit (LR p =0.06). When BR was included in the hip model, the BR estimate was not significant (OR=0.69, 95%CI=0.40,1.18), and the strength of the DXA-derived T-score again increased (OR=0.20, 95%CI=0.03,1.12), though model fit was not improved (LR p=0.14).

Conclusions: Novel radiologic parameters such as HRpQCT-derived tvBMD and HSA-derived BR may aid in identifying correlates of low-trauma fracture in HIV patients, and warrant further study as supplementary markers of fracture risk in HIV clinical trials.

WEDNESDAY, FEBRUARY 25, 2015

Session P-Q5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Fat Without Borders: Metabolic Complications in Resource-Limited Settings

778 Obesity and Inflammation in Resource-Diverse Settings of ART Initiation

Kristine M. Erlandson[1]; Nikhil Gupte[2]; Javier R. Lama[3]; Patcharaphan Sugandhavesa[4]; Thando Mwelase[5]; Ashwin Balagopal[2]; David Asmuth[6]; Thomas B. Campbell[1]; Amita Gupta[2]
On behalf of the A5175 and NWCS319 study team

[1]University of Colorado, Aurora, CO, US; [2]Johns Hopkins University, Baltimore, MD, US; [3]Impacta Peru Clinical Trials Unit, Lima, Peru; [4]Chiang Mai University, Chiang Mai, Thailand; [5]University of Witswatersrand, Johannesburg, South Africa; [6]University of California Davis, Sacramento, CA, US

Background: The heightened inflammatory profile resulting from both HIV infection and obesity is of increasing importance in many HIV-related comorbidities. Little is known about the association between the change in body mass index (BMI) with antiretroviral (ART) initiation and the change in inflammatory markers, particularly in resource-limited settings.

Methods: AIDS Clinical Trials Group study A5175 was a randomized trial comparing 3 ART regimens in resource-diverse international settings; the following is a country stratified random sub-cohort of 270 subjects; 246 subjects had stored samples. BMI (weight [kg]/height [m]^2) was categorized as underweight (UW, <18.5), normal weight (NW, 18.5-24.9), and overweight/obese (OW/OB, ≥25.0). Inflammatory markers were measured (TNF-α, IFN-γ, IL-6, IL-18, IP-10, CRP, sCD14) at weeks 0, 24, 48. Effect of baseline and change in BMI on changes in biomarkers was assessed using random effects models fitted for natural spline at BMI categories and adjusted for age, sex, country, $\log_{10}$ HIV-1 RNA, and treatment arm. A separate model assessed the effect of change to OB BMI (>30 versus ≤30).

Results: Of 246 participants, 50% were female, 53% black, with a median age 35 and CD4 count 179. 37% were assigned to ZDV/3TC+EFV, 33% to ATV+FTC+DDI, and 30% to TDF/FTC+EFV. At week 0, 8% were UW, 65% NW, 27% OW/OB including 7% OB; at week 48, 3% were UW, 60% NW, 37% OW/OB including 9% OB. In multivariate analyses, among baseline UW subjects, an incremental BMI increase was associated with decreased CRP (β -9.32; p=0.001) and trend towards decreased sCD14 (β -0.09; p=0.09). For baseline OW/OB subjects, an increase in BMI was associated with increased sCD14 (β 0.02; p=0.05). No significant associations were detected in the NW group or within other inflammatory markers (p>0.05). In multivariate analyses comparing OB vs not OB participants, OB was associated with an increase in sCD14 (β 0.19; p=0.02) and trend towards higher IL-18 (β 127.7; p=0.056); there were no associations with other markers.

Conclusions: Among HIV-infected persons initiating ART in resource-diverse settings, weight gain among underweight persons may reduce inflammation. In contrast, weight gain among obese persons appeared to heighten inflammation. As sCD14 is a marker of mortality during HIV treatment, the data highlight the potential impact of obesity on treatment outcomes. Further investigation into the impact of obesity on HIV treatment outcomes in resource-limited settings is needed.

779 Body Composition Outcomes at 96 Weeks in the SECOND-LINE RCT DXA Substudy

Mark A. Boyd[1]; Janaki Amin[1]; Patrick W. Mallon[2]; Jennifer F. Hoy[3]; Samuel Ferret[4]; Waldo Belloso[5]; Praphan Phanuphak[6]; Sean Emery[1]; David A. Cooper[1]
SECOND-LINE study group

[1]University of New South Wales Australia, Sydney, Australia; [2]University College Dublin, Dublin, Ireland; [3]Monash University/Alfred Hospital, Melbourne, Australia; [4]Hopital Saint Louis, Paris, France; [5]Hospital Italiano, Buenos Aires, Argentina; [6]Thai Red Cross AIDS Research Centre, Bangkok, Thailand

Background: Antiretroviral therapy (ART) should optimally cause minimal harm. Preferred N(t)RTI-backbones are associated with toxicities with poorly understood long term consequences. In the SECOND-LINE study we demonstrated non-inferiority (margin=12%) of ritonavir-boosted lopinavir (r/LPV) plus raltegravir (RAL-arm) compared to r/LPV plus 2-3N(t)RTI regimen (N(t)RTI-arm) after virological failure of standard NNRTI+2N(t)RTI first-line ART. The RAL-arm was associated with significantly less bone mineral density (BMD) loss. We hypothesised that the RAL-arm would be associated with a greater degree of limb fat gain at 96 weeks.

Methods: We performed a DXA-substudy of SECOND-LINE at weeks 0, 48 and 96 at 8 sites in Argentina, India, Malaysia, South Africa and Thailand. Primary endpoint was the mean percent change from baseline in peripheral limb fat. Analysis was by intention to treat (ITT). We adjusted for baseline imbalances in sex, BMI and smoking. Multivariate linear regression was used to assess between-group differences and predictors of percent change in limb fat mass. Results are mean (SD) and median (IQR).

Results: Baseline characteristics of the 210 enrolled participants: 110 (52%) female, age 38.6 (7.8) years, 52% Asian/43% African, HIV RNA 4.1 (1.0) $\log_{10}$ copies/mL, CD4+ count 220 (167) cells/μL, first-line ART duration 3.3 (1.9-5.9) years, 34%% and 48% on d4T and AZT respectively prior to initiating randomised ART. Eighty six percent and 42% N(t)RTI arm study participants received TDF and AZT respectively. After 96 weeks the mean (SD)% limb fat change from baseline was 16.8 (32.6)% in the N(t)RTI-arm and 28.0 (37.6)% in the RAL-arm, a mean difference (95% CI) of 10.2 (0.1-20.4)% (p=0.048). Baseline predictors of percent changes in limb fat mass over 96 weeks are shown in Table 1.

Table 1. Multivariate baseline predictors of percent change in limb fat mass over 96 weeks

Covariate		Reference	N	Coefficient	95% CI	P-value	Overall p-value
Study arm	RAL-arm	*N(t)RTI-arm*	105	4.9	-2.6, 12.5	0.2	
Sex	Female	*Male*	101	15.0	4.2, 25.9	0.007	
BMI (kg/m^2)			192	1.5	0.5, 2.5	0.005	
BMI change over 96 weeks (kg/m^2)			192	8.4	6.9, 9.8	<0.001	
Baseline limb fat mass (kg)							
	3.9 - 6.9	*0.7 - 3.89*	45	-19.6	-30.8, -8.4	0.001	
	7.0 - 11.0	*0.7 - 3.89*	49	-36.4	-50.0, -22.8	<0.001	
	11.1 - 32.0	*0.7 -3.89*	52	-28.1	-76.8, -41.2	<0.001	<0.001
Ethnicity							
	African	*Asian*	83	-9.8	-19.5, -0.1	0.048	
Total ta-NRTI (AZT/d4T) duration prior to study (years)			192	-4.0	-8.0, 0.02	0.051	

Conclusions: Although N(t)RTI-sparing in SECOND-LINE was associated with improved peripheral limb fat gain over 96 weeks, it was not significant after adjustment for other predictors on multivariate analysis. Significant predictors of peripheral fat gain were female sex, higher baseline BMI and a greater increase in BMI. Africans were more likely to lose limb fat than Asians. Those with more limb fat at baseline were more likely to lose limb fat over 96 weeks. Thymidine-analogue duration prior to study had a borderline association with less peripheral fat gain.

780 Bone Quality by Quantitative Ultrasound at the Radius Does Not Differ in ART-Naïve HIV+ and HIV- Rwandan Women

Eugene Mutimura[1]; Qiuhu Shi[2]; Donald R. Hoover[3]; Kathryn Anastos[4]; Emmanuel Rudakemwa[5]; Jean Claude Dusingize[1]; Jean D'Amour Sinayobye[1]; Michael T Yin[6]

[1]Regional Alliance for Sustainable Development, Kigali, Rwanda; [2]School of Health Sciences and Practice, New York Medical College, New York, NY, US; [3]State University of New Jersey, New Brunswick, NJ, US; [4]Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, US; [5]King Faisal Hospital, Kigali, Rwanda; [6]Columbia University Medical Center, New York, NY, US

Background: Fracture incidence appears to be increased in HIV+ individuals, especially after ART. Dual-energy x-ray absorptiometry (DXA) characterizes bone mineral density (BMD) and is predictive of fracture, but is not widely available in resource-constrained settings (RCS). Quantitative ultrasound (QUS) assesses bone quality by measuring speed of an ultrasound wave (SOS) through bone; lower SOS is predictive of increased fracture risk in older women. We compared bone quality by QUS at the radius in HIV+ and HIV- women in Rwanda.

Methods: Cross sectional study of 646 ART-naïve HIV+ and 211 HIV- women. Demographic, anthropomorphic, laboratory, co-morbidity, and socioeconomic data were collected. A Sunlight Omnisense 7000 QUS (BeamMed Ltd, Israel) was utilized to measure SOS at the radius using 2 trained technicians. Inter-observer agreement assessed on a subset (N=56) was high (kappa>0.90). Mean SOS±SD, T-scores (compared to SOS from young women), Z- scores (compared to SOS from women of same age) using the manufacturer's reference based upon American norms were calculated.

Results: HIV+ women were younger than HIV- women (35±7 vs 42+10 years, p<0.001), had more chronic diarrhea (23% vs 8%, p<0.001), and lower albumin (3.4±0.7 vs. 3.9±0.5 g/dL, p<0.001), but similar body mass index (BMI, 21.5±3.7 vs 21.3±3.8 kg/m^2, p=0.51). Among HIV+ women, mean CD4+ T cell count was 285 (SD=166) cells/mm^3 and 30% had an AIDS defining illness. Average SOS was slightly higher in HIV+ than HIV- women (4024.4±110.5 vs. 4003.9±113.1 m/s, p= 0.02); this group difference was attenuated by adjustment for age (p=0.04) but not BMI (Table). SOS T- and Z-scores did not differ pre or post adjustment for BMI between HIV infection groups. Among HIV+ women, SOS did not differ by CD4+ count <200 vs. ≥200cells/mm^3: 4016±117 vs 4028±107m/s, respectively (p=0.19).

Bone Quality by Quantitative Ultrasound among ART-naïve HIV+ and HIV- Rwandan women

Characteristics	HIV+ (N=646)	HIV- (N=211)	P value	P value Adjusted for Age	P value Adjusted for BMI
Average SOS (m/s)	4024.4±110.5	4003.9±113.1	0.02	0.04	0.02
T score	-0.07±1.37	-0.18±1.43	0.30	-	0.31
Z score	0.09±1.35	0.10±1.38	0.90	-	0.89

Data are presented as Mean±SD; *The p-value is from ANOVA; ART, antiretroviral therapy; HIV+, HIV-infected; HIV, HIV-uninfected; BMI, Body mass index; SOS, ultrasound wave.

Conclusions: Despite having relatively advanced HIV disease, ART-naïve, predominantly premenopausal Rwandan women did not have worse bone quality by radius QUS than uninfected controls. Our results are consistent with data from a South African study that found that BMD by DXA were similar in ART-naïve HIV+ women and uninfected controls. Unlike DXA, radius QUS is uninfluenced by weight or body fat, is portable, inexpensive, and does not emit radiation or require high-level training. QUS may be an ideal modality to track bone quality and fracture risk after ART-initiation in HIV+ individuals in RCS.

781 Predictors and Outcomes of Incident High Cholesterol in Adults on ART in South Africa

Denise Evans[1]; Alana T. Brennan[2]; Faith Moyo[1]; David Spencer[3]; Kay Mahomed[3]; Mhairi Maskew[1]; Lawrence Long[1]; Sydney Rosen[2]; **Matt P. Fox**[2]

[1]University of the Witwatersrand, Johannesburg, South Africa; [2]Boston University, Boston, MA, US; [3]Right to Care, Johannesburg, South Africa

Background: As the HIV-infected population ages in sub-Saharan Africa, non-communicable chronic disease incidence among patients on ART is likely to rise. Specific antiretroviral drugs are considered independent risk factors for cardiovascular disease (CVD), and high total cholesterol (TC) is a risk factor for CVD, stroke and renal disease. We examined predictors of high TC in ART patients in South Africa.

Methods: Prospective study of HIV-positive, ART-naïve adults initiating ART at a large urban clinic in Johannesburg from 04/04 to 07/12. Patients with TC ≥6mg/dl at ART initiation were excluded. We defined incident high cholesterol as a TC ≥6mg/dl and categorized it as (i) one elevated TC, (ii) elevated TC with repeat TC <6mg/dl or (ii) elevated TC with repeat ≥6mg/dl. Cox regression was used to identify variables at ART initiation associated with incident high TC. Person-time started at ART initiation and ended at the earliest of high TC, death, loss to follow up (LTF; >3 months late for next scheduled visit), transfer, completion of 24 months of follow-up, or dataset closure (07/2014).

Results: Among 18,998 eligible patients, 2990 (16%) had a high TC by 24 months on ART. Of these, 488 (16%) had no repeat TC, 1323 (44%) had a repeat TC <6mg/dl, and 1179 (40%) had a persistently high TC ≥6mg/dl. Regression models showed patients ≥40 vs. <40 years, those with a CD4 count <100 vs. ≥100cells/mm^3 or BMI ≥25 vs. <25kg/m^2 at ART initiation had an increased hazard of high TC over the first 24 months on ART (Table).

Of the 2990 patients with a high TC, 5% died, 7% were LTF and 11% developed moderate or severe renal insufficiency (creatinine clearance <60ml/min). Among those with a repeat TC, rates of mortality (0.82 vs. 0.83/100pys) and LTF (6.1 vs. 7.3/100pys) after high TC were similar for those with incident high TC and a repeat TC <6mg/dl compared to those with a persistently high TC ≥6mg/dl. However, those with persistently high TC ≥6mg/dl had a higher rate of renal insufficiency (CrCl <90ml/min) (19.0/100pys) after high TC compared to those who reduced their TC <6mg/dl (16.0/100pys). 31% of patients with a high TC changed a single drug, mainly from d4T to TDF or ABC, while 29% were prescribed cholesterol lowering drugs and 13% had both.

Table 1. Predictors of high total serum cholesterol after 24 months on antiretroviral therapy at Themba Lethu Clinic, Johannesburg, South Africa (n=18,998).

		One elevated TC		Elevated TC + repeat <6mg/dl		Elevated TC + repeat ≥6mg/dl	
		No. Events N, %	Adjusted HR 95% CI	No. Events N, %	Adjusted HR 95% CI	No. Events N, %	Adjusted HR 95% CI
Initiating NRTI	TDF	147 (2.9%)	1.0	171 (3.4%)	1.0	130 (2.6%)	1.0
	d4T	327 (2.5%)	0.86 (0.67-1.10)	1114 (8.4%)	2.41 (1.99-2.96)	1026 (7.7%)	3.48 (2.73-4.44)
Initiating NNRTI	EFV	433 (2.6%)	1.0	1170 (6.9%)	1.0	1075 (6.4%)	1.0
	NVP	39 (3.0%)	1.16 (0.79-1.69)	95 (7.3%)	1.00 (0.79-1.27)	62 (4.7%)	0.83 (0.62-1.10)
Age at ART initiation (years)	18-29.9	79 (2.1%)	1.0	204 (5.4%)	1.0	133 (3.5%)	1.0
	30-39.9	188 (2.2%)	1.08 (0.78-1.39)	587 (7.0%)	1.19 (1.00-1.41)	428 (5.1%)	1.44 (1.16-1.79)
	≥40	221 (3.3%)	1.68 (1.26-2.24)	530 (7.9%)	1.57 (1.31-1.87)	618 (9.2%)	2.88 (2.33-3.56)
Sex	Female	312 (2.6%)	1	884 (7.5%)	1.0	772 (6.5%)	1.0
	Male	176 (2.5%)	0.99 (0.80-1.22)	439 (6.1%)	0.89 (0.78-1.02)	407 (5.7%)	0.88 (0.77-1.01)
Body mass index (kg/m²)	<18	46 (1.8%)	0.80 (0.57-1.12)	127 (4.8%)	0.81 (0.66-0.99)	97 (3.7%)	0.65 (0.52-0.82)
	18-24.9	272 (2.7%)	1.0	693 (6.9%)	1.0	631 (6.3%)	1.0
	25-29.9	96 (3.4%)	1.29 (1.00-1.66)	292 (10.2%)	1.54 (1.33-1.79)	261 (9.1%)	1.45 (1.24-1.70)
	≥30	49 (3.5%)	1.31 (0.93-1.85)	134 (9.5%)	1.47 (1.19-1.81)	125 (8.9%)	1.55 (1.25-1.92)
CD4 count (cells/mm³)	>200	92 (3.2%)	1.0	167 (5.9%)	1.0	143 (5.0%)	1.0
	101-200	177 (2.8%)	0.98 (0.75-1.29)	459 (7.3%)	1.15 (0.95-1.40)	411 (6.5%)	1.07 (0.87-1.32)
	51-100	70 (2.0%)	0.70 (0.50-0.99)	295 (8.4%)	1.41 (1.14-1.74)	240 (6.8%)	1.19 (0.95-1.49)
	0-50	134 (2.5%)	1.06 (0.89-1.42)	372 (6.8%)	1.36 (1.11-1.66)	358 (6.6%)	1.39 (1.13-1.72)
Hemoglobin (g/dl)	≥10	365 (2.8%)	1.0	998 (7.7%)	1.0	892 (6.9%)	1.0
	<10	86 (2.0%)	0.98 (0.77-1.27)	236 (5.5%)	0.85 (0.73-1.00	210 (4.9%)	0.57 (0.74-1.02)
WHO stage	I/II	332 (2.9%)	1.0	837 (7.8%)	1.0	731 (7.1%)	1.0
	III/IV	156 (2.1%)	1.03 (0.81-1.30)	486 (7.2%)	1.14 (0.99-1.30)	448 (6.0%)	1.00 (0.87-1.17)

TC Total Cholesterol; NRTI Nucleotide Reverse Transcriptase Inhibitors; NNRTI Non-nucleoside reverse-transcriptase inhibitors; HR Hazard Ratio; CI Confidence interval; d4T stavudine; TDF tenofovir; EFV efavirenz; NVP nevirapine

Conclusions: Older patients, those on stavudine, those overweight or with low CD4 counts should be targeted for frequent TC monitoring and identification of other risk factors of CVD in order to implement lifestyle modifications and pharmaceutical therapy.

782 Metabolic Changes and Second-Line ART in Africa (2LADY/ANRS 12169 Trial)

Amandine Cournil[1]; Assane Diouf[5]; Sabrina Eymard-Duvernay[1]; Adrien Sawadogo[2]; Liliane Ayangma[4]; Louise Fortes-Deguenonvo[3]; Jean-Marc Mben[6]; Eric Delaporte[1]; Laura Ciaffi[1]; Sinata Koulla-Shiro[5]

[1]IRD/UM 1, Montpellier, France; [2]CHU Souro Sanou, Bobo Dioulasso, Burkina Faso; [3]CRCF, Dakar, Senegal; [4]Yaounde Military Hospital, Yaounde, Cameroon; [5]FMSB/University Yaounde 1, Yaounde, Cameroon; [6]ANRS Research Center, Yaounde, Cameroon

Background: Beyond efficacy, information about the impact on metabolism of 2nd line antiretroviral combinations can be of value in the evaluation of long term benefit of treatment in the African context.

The aim was to compare changes over 48 weeks in metabolic profile of three second line regimens within the randomized 2LADY/ANRS 12169 trial (Yaounde, Cameroon; Bobo Dioulasso, Burkina Faso; Dakar, Senegal).

Methods: 451 HIV-1 positive adults, failing standard first line ART were randomized to tenofovir disoproxil fumarate (TDF) + emtricitabine (FTC) + lopinavir/ritonavir (LPV/r) [reference]; abacavir (ABC) + didanosine (ddI) + LPV/r [ABC/ddI] or TDF + FTC + darunavir (DRV) /r [DRV]. Cardiovascular disease (CVD) risk factors considered were obesity or overweight (Body Mass Index (BMI)≥25kg/m²); hypercholesterolemia (≥200mg/dL); hypertriglyceridemia (≥150mg/dL); hypertension (≥130/85mmHg) and metabolic syndrome according to IDF/AHA/NHLBI criteria.

Results: 432 (71% women) patients with a median age of 38 years were analyzed. At entry, the median CD4 count was 183 cells/μl; (IQR: 90-290), 32% were obese or overweight; and 11% had metabolic syndrome with no difference between arms.

The mean weight gain (kg) over 48 weeks was significantly greater in DRV group (+3.0±4.9) than in reference (+0.7±5.2) and in ABC/ddI groups (+0.8±4.7). In DRV group, over 48 weeks 26% of patients increased BMI from normal to overweight or obese.

In contrast, the ABC/ddI compared with DRV group had greater mean increases (mg/dL) in triglycerides (+33±68 vs -6±60; P<0.01) and in cholesterol (+30±53 vs -1±43 ; P<0.001) with significant increases in both HDL- and LDL-cholesterol. Over 48 weeks a significantly higher proportion of patients developed hypercholesterolemia, hypertriglyceridemia and metabolic syndrome in the ABC/ddI compared with DRV group. CVD risk factors did not differ between DRV and reference group.

Lipids levels changes and incidence of metabolic syndrome remained independently associated with treatment regimen in multivariable analyses including baseline clinical and metabolic variables.

Cumulative incidence at week 48	TDF+FTC+LPV/r "Reference" n = 146	ABC+ddI+LPV/r "ABC/ddI" n = 138	TDF+FTC+DRV/r "DRV" n = 148	P
Overweight/obesity	17/106 (16%)	7/84 (8%)	25/97 (26%)	<0.01
Hypercholesterolemia	27/108 (25%)	38/88 (43%)	20/99 (20%)	<0.001
Hypertriglyceridemia	18/125 (14%)	27/112 (24%)	11/125 (9%)	<0.01
Hypertension	11/112 (10%)	14/98 (14%)	13/114 (11%)	0.60
Metabolic syndrome	10/130 (8%)	18/116 (15%)	5/119 (4%)	<0.01

Both efficacy (CROI2014) and metabolic tolerance results at 48 weeks indicate that the recommended WHO regimen remains a valid option.

Conclusions: Despite a marked weight gain with high incidence of overweight and obesity in the DRV group, the most worrying changes in metabolic profile were observed in the ABC/ddI group with important increase in CVD risk factor which could compromise the long term benefit of this combination

TUESDAY, FEBRUARY 24, 2015

Session P-Q6 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Aging: Frailty, Telomeres, and mtDNA

783 Frailty and Cause-Specific Hospitalization Among Persons Aging With HIV and Drug Use

Damani A. Piggott[1]; Abimereki D. Muzaale[1]; Shruti H. Mehta[1]; Ryan P. Westergaard[2]; Todd T. Brown[1]; Kushang V. Patel[3]; Sean X. Leng[1]; Gregory D. Kirk[1]

[1]Johns Hopkins University, Baltimore, MD, US; [2]University of Wisconsin, Madison, WI, US; [3]University of Washington, Seattle, WA, US

Background: Hospitalization events exact a substantial economic and clinical burden for aging HIV-infected populations. Frailty is a key aging-related syndrome, predictive of major adverse clinical outcomes, including all-cause hospitalization among older HIV-uninfected adults. We have previously reported the association of frailty with advanced HIV and mortality; however, limited data exist on the relationship of frailty to hospitalizations due to infectious or non-infectious causes among HIV-infected persons or their uninfected counterparts.

Methods: Frailty was ascertained in the ALIVE cohort of persons with prior or current injection drug use based on the 5 Fried phenotype criteria. Hospitalization events were ascertained from 2005-2012 and categorized using Agency for Healthcare Research and Quality clinical classification software into: chronic disease, infectious disease, and non-chronic non-infectious conditions. Cox proportional hazards models were used to estimate the risk (hazard ratios [HR] with 95% confidence intervals [CI]) for time to first hospitalization for each category.

Results: Among 1303 participants with a median age of 48 years, 32% were HIV infected, and 12% were frail. In multivariable models adjusting for age, sociodemographics, comorbidity, substance use, and HIV/AIDS status, frailty was significantly associated with chronic disease (aHR 2.03; 95% CI, 1.40, 2.96), and infectious disease (aHR 2.41; 95% CI, 1.54, 3.76) hospitalization; but not with non-chronic non-infectious hospitalization (aHR 1.07; 95% CI, 0.72, 1.59). A prior AIDS diagnosis was associated with increased hospitalization risk in all 3 categories. Among HIV-infected persons, independent of CD4 count, HIV viral load, or prior AIDS, frailty was significantly associated with increased AIDS hospitalization risk (aHR 6.30; 95% CI, 1.20, 33.1). Frailty was also independently associated with non-AIDS infectious disease hospitalization risk (aHR 2.21; 95% CI, 1.40, 3.50).

Conclusions: The frailty phenotype selectively predicts vulnerability to chronic disease and infectious disease related hospitalization, independent of comorbidity, degree of HIV immunosuppression and virologic control. Frail persons are susceptible to increased hospitalization for both AIDS and Non-AIDS infection. Further elucidation of frailty pathways may facilitate targeted interventions to reduce health care utilization and improve clinical management for aging HIV-infected persons and their high risk counterparts.

784 Association of HIV Viral Load and Shorter Telomere Length

Shawn Gogia; Jue Lin; Yifei Ma; Rebecca Scherzer; Elizabeth Blackburn; Ramin Farzaneh-Far; Steven Deeks; Priscilla Hsue

University of California San Francisco, San Francisco, CA, US

Background: Telomeres are DNA sequences on the ends of chromosomes that protect genomic integrity and shorten as cells age. Telomerase counteracts telomere shortening and prevents cellular aging. Telomerase may be inhibited by reverse transcriptase inhibitors and telomeres in T cells may be shortened by excess HIV-associated proliferation. Given association of HIV with CVD and other conditions associated with aging, we initiated systematic studies of telomere length (TL), telomerase activity (TA) and vascular function in a diverse cohort of HIV-infected and uninfected adults.

Methods: We measured TL, TA, and endothelial function in 65 HIV-infected and 24 uninfected controls. Mean PBMC TL was measured from DNA using qPCR and TA was assessed using the Gel-TRAP assay. Endothelial function was measured using flow-mediated vasodilation of the brachial artery (FMD). Generalized linear regression models with log link function were used to compare levels of TL and TA and to identify associated factors.

Results: HIV+ and control subjects had similar demographic and traditional CVD risk factors. Median TL was 0.95 in treated and virally suppressed patients and 0.93 in untreated and non-suppressed, compared with 1.07 in uninfected controls ($p=0.046$), while median TL was 1.02 in untreated, virally suppressed patients ($p=0.72$ vs. controls). TL remained 12% shorter ($p=0.004$) in untreated individuals with detectable viremia compared with controls after adjustment for age, gender, and race. Among HIV patients, age (10% shorter per decade, $p<0.001$), viral load >10K copies/mL (21% shorter vs VL<2K, $p<0.001$), and higher sCD163 (9% shorter per doubling, $p=0.018$) were independently associated with shorter TL. Correlations with FMD were weak for both TL ($r=0.12$, $p=0.34$) and TA ($r=0.11$, $p=0.46$).

Conclusions: HIV+ individuals have shorter TL compared to controls, a finding that appears to be driven by HIV replication. In particular, we found that having an HIV RNA level >10,000 copies/ml was associated with a larger reduction in TL than a decade of aging. Higher sCD163, a marker of monocyte/macrophage activation, was also independently associated with shortened TL. These data support the concept that HIV compromises telomere maintenance, perhaps with partial reversal by ART. Because TL and TA may also be influenced by monocyte/macrophage activation and other processes, larger studies are necessary to define the role of TL and telomerase in HIV+ persons.

785 Novel Mechanisms of Nucleoside Analog Associated Mitochondrial DNA Mutation

Kristian Gardner; Patrick F. Chinnery; **Brendan A. Payne**

Newcastle University, Newcastle-upon-Tyne, United Kingdom

Background: Mitochondrial DNA (mtDNA) mutation is a key feature of human aging. NRTI therapy may lead to accelerated accumulation of mtDNA mutations, but the mechanisms are unknown.

Methods: We used a transmitochondrial cybrid cell line containing a single 7.5kb mtDNA deletion mutation, and fibroblasts from elderly individuals containing the m.414T>G point mutation. Cells were exposed to NRTIs for 32 days. MtDNA content was determined by multiplex real-time PCR. Deletion mutations were analysed by multiplex real-time PCR and long-range PCR. Point mutations were analysed by pyrosequencing (Qiagen) and massively parallel resequencing (Illumina MiSeq).

Results: In ddI-treated cybrids, heteroplasmy level of the deletion mutation increased from 75% to 96% (SD 1.6%, $p<0.01$). This was due to selective depletion of wild-type mtDNA content (to 14% of baseline, SD 3%, $p<0.001$) but preservation of mutant mtDNA. Cybrids treated with physiological doses of d4T, AZT or TDF showed no significant changes in deletion heteroplasmy, however 10x physiological dose d4T did increase heteroplasmy to 86% (SD 4%). There was no evidence of new deletion mutation formation with any NRTI at normal or 10x dosing.

In fibroblasts there was no significant change in the heteroplasmy level (~50%) of the m.414T>G point mutation with any of the NRTI exposures. However deep resequencing revealed multiple additional low-level (<5% heteroplasmy) point mutations. When subjected to mtDNA depletion (due to ddI), followed by repopulation of mtDNA content (i.e. a molecular bottleneck), significant shifts in low-level mutations were seen (ddI, mean shift 6.3%, SD 2.8%; untreated, mean 2.7%, SD 1.2%; $p=0.01$). This effect was accentuated with 10x physiological dose ddI exposure. No significant heteroplasmy shifts were seen with d4T, AZT or TDF. There was no new point mutation formation.

Conclusions: Despite prolonged and high-dose exposure to NRTIs, there is no mutagenesis in mtDNA. However, we observed: 1) a selective advantage to the replication of deleted mtDNA (ddI and high-dose d4T); and 2) the enhanced segregation of mtDNA point mutations through a molecular bottleneck mechanism (ddI). Both phenomena will *in vivo* lead to accelerated clonal expansion of pre-existing (age-associated) mtDNA mutations within individual cells. These data provide a plausible mechanism for increased mtDNA mutations observed in NRTI-treated patients. Such mutations may lead to accelerated physiological decline during aging.

786 Balance Confidence Predicts Falls Better Than Physical Function Testing in HIV+ Men

Todd T. Brown[1]; Xiuhong Li[2]; Lisa P. Jacobson[2]; Jennifer Schrack[2]; Frank J. Palella[3]; Lawrence Kingsley[4]; Joseph B. Margolick[2]; Adrian Dobs[1]; Jordan Lake[5]; Keri N. Althoff[2]
MACS

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [4]University of Pittsburgh, Pittsburgh, PA, US; [5]University of California Los Angeles, Los Angeles, CA, US

Background: Falls are a major source of morbidity in older adults. Tests of physical function and questionnaires of self-reported balance confidence have been used to predict fall risk in older HIV-uninfected (HIV-) persons, but these assessments have not yet been validated in HIV-infected (HIV+) persons.

Methods: HIV+ and HIV- men who have sex with men 50-70 years old were recruited from the Multicenter AIDS Cohort Study (MACS) for a substudy assessing fracture risk. At baseline, participants underwent clinical tests of balance (Functional Reach Test, Standing Balance Test), strength (grip strength, chair stands), gait speed, composite measurements of physical function (Short Physical Performance Battery), and a short questionnaire assessing balance confidence during various activities (Activities Balance Confidence (ABC), which assesses balance confidence on a scale of 0-100% during 6 activities (<80%=low confidence)). Falls were reported prospectively over a two-year period (median follow up time (IQR) 14.7 (12.3-16.5) months). The relationships between clinical tests of physical function/ABC and falling status (faller vs non-faller) were determined with logistic regression. All analyses were adjusted for age, race, education, body mass index, MACS site, and HIV serostatus.

Results: During the follow-up period, 27% (65/238) of HIV+ men and 23% (69/298) of HIV- men reported at least one fall (p=0.28); 11% of HIV+ men and 9% of HIV- men reported ≥2 falls (p=0.40). Overall, lower balance confidence (<80% vs ≥ 80% on ABC) was significantly associated with having a fall (adjusted odds ratio (aOR) 2.24 [95% confidence interval (CI); 1.38, 3.66]). In contrast, lower performance on physical function tests showed no association with falling(p>0.099 for each test). Similar results were observed for the relationship of these assessments with having 2 or more falls. Among the HIV+ men, lower balance confidence also predicted falling (aOR 4.25 (95%CI:1.93, 9.35), p<0.001), but physical function tests did not (p>0.07 for each test).

Conclusions: HIV serostatus was not associated with incident falls in this population of older men. Self-reported balance confidence was a significantly better predictor of falls than standard clinical tests of strength and balance, and could be easily incorporated into clinical practice to identify HIV-infected patients at greater risk of falls.

TUESDAY, FEBRUARY 24, 2015

Session P-Q7 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Diabetes and Other Endocrine Disorders

787 Vitamin D Supplementation Does Not Affect Metabolic Changes Seen With ART Initiation

Todd T. Brown[1]; Ellen Chan[2]; Edgar T. Overton[3]; Pablo Tebas[4]; Kathy Melbourne[5]; Royce Hardin[6]; Heather Ribaudo[2]; Michael T. Yin[7]
ACTG

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]University of Alabama at Birmingham, Birmingham, AL, US; [4]University of Pennsylvania, Philiadelphia, PA, US; [5]Gilead Sciences, Inc., Foster City, CA, US; [6]Duke University, Durham, NC, US; [7]College of Physicians and Surgeons, Columbia University, New York, NY, US

Background: Insulin resistance and lipid changes are commonly seen after ART initiation. Observational studies suggest that vitamin D supplementation reduces the risk of developing diabetes and improves lipid profiles.

Methods: This 48-week prospective, randomized, double-blind, placebo-controlled study evaluated the effect of high dose vitamin D3 (4000 IU daily) plus calcium supplementation (1000 mg calcium carbonate daily) in HIV-infected subjects initiating ART with efavirenz/emtricitabine/tenofovir. In this secondary analysis, changes in insulin resistance (as measured by HOMA-IR), lipid profile, and components of the metabolic syndrome were assessed at baseline, 24 and 48 weeks using the intent-to-treat approach. Stratified Wilcoxon rank sum tests and stratified normal score tests were used to test for differences between the two treatment groups, stratified by screening 25-OH vitamin D stratum (≤/> 20 ng/mL). A more conservative significance level 0.01 was used in order to adjust for multiple testing.

Results: 165 eligible subjects enrolled, with 79 in Vitamin D/Calcium (Vit D/Cal) group and 86 in placebo group. The placebo group but not the VitD/Cal group experienced modest increase in insulin resistance at week 24 (P<0.001). While increases in total and HDL cholesterol were apparent in both groups at weeks 24 and 48, increases in LDL cholesterol at week 24 were only marginal in the placebo group (P=0.011). BMI was stable over the course of the study, whereas modest increases in waist circumference were observed at week 24 that were not persistent at week 48. Metabolic syndrome was present in 19 subjects (12%) at baseline and 20 subjects (14%) at week 48 without differences between groups. There were no between group differences in any of these metabolic parameters at either 24 or 48 week evaluations (P≥0.17).

Parameter	Baseline Values			Week 24 Values			Week 48 Values		
	n	VitD/Cal	Placebo	n	VitD/Cal	Placebo	n	VitD/Cal	Placebo
HOMA-IR	150	0.97 (0.52, 2.12)	0.94 (0.46, 1.81)	142	1.31 (0.69, 2.24)	**1.49 (0.91, 2.52)**	133	1.30 (0.81, 2.69)	1.43 (0.82, 2.49)
Total Chol (mg/dL)	162	161 (138,182)	156 (135,184)	154	**167 (151,192)**	**174 (154,201)**	141	**167 (151,191)**	**170 (152,192)**
HDLc (mg/dL)	155	43 (34,50)	42 (33,49)	145	**47 (41,59)**	**49 (39, 61)**	134	**49 (40,58)**	**50 (39,60)**
LDLc (mg/dL)	154	95 (80,112)	89 (72,115)	142	97 (78,115)	99 (79,124)	132	99 (84,115)	98 (79,116)
Triglycerides (mg/dL)	160	99 (65,127)	96 (73,116)	152	96 (72,140)	93 (73,140)	139	101 (77,147)	97 (68,142)
BMI (kg/m^2)	160	25.7 (22.6,28.2)	24.0 (21.6,27.1)	155	25.6 (22.7,27.9)	23.5 (21.0,27.4)	146	25.5 (22.7,29.0)	23.6 (21.3,27.8)
Waist circ (cm)	163	88.3 (81.3,97.8)	84.1 (79.1,94.0)	161	87.0 (81.0,98.4)	**86.3 (78.1,95.3)**	148	89.6 (83.0,98.8)	86.7 (79.1,97.3)
Metabolic Syndrome	161	7 (9%)	12 (14%)	149	7 (10%)	11 (14%)	141	9 (14%)	11 (15%)

All values given as median (Q1,Q3) except metabolic syndrome.

Shaded boxes with bolded text denote a significant change in parameter from baseline (P<0.01).

NOTE: There were no significant between group changes at either time point (P≥0.17 for all).

Conclusions: Vit D/Cal supplementation over 48 weeks did not attenuate increases in insulin resistance with initiation of efavirenz/emtricitabine/tenofovir in ART-naïve persons. The prevalence of metabolic syndrome did not increase significantly over the course of follow up. Vitamin D supplementation had minimal impact on metabolic parameters with ART initiation.

788 First-Line NRTIs and Risk of New Onset Diabetes in HIV-Infected Adults in Thailand

Prakit Riyaten[1]; Nicolas Salvadori[2]; Patrinee Traisathit[1]; Nicole Ngo-Giang-Huong[2]; Rapeepan Suaysod[2]; Guttiga Halue[3]; Naruepon Yutthakasemsunt[4]; Apichat Chutanunta[5]; Jacqueline Capeau[6]; Gonzague Jourdain[2]

[1]Chiang Mai University, Chiang Mai, Thailand; [2]Institut de Recherche Pour le Développement UMI 174-PHPT, Chiang Mai, Thailand; [3]Phayao Provincial Hospital, Phayao, Thailand; [4]Nong Khai Hospital, Nong Khai, Thailand; [5]Samutsakhon Hospital, Samutsakhon, Thailand; [6]Sorbonne University, Paris, France

Background: Exposure to some antiretrovirals (ARVs), in particular thymidine analogue nucleosides, has been associated with a higher risk of diabetes. However, this risk may vary according to ARVs and combinations. We estimated the risk of new onset diabetes in a large HIV-infected adult cohort in Thailand and studied the impact of four different nucleos(t)ide reverse transcriptase inhibitors (NRTIs) containing first-line regimens.

Methods: We selected all HIV-1 infected, antiretroviral therapy (ART)-naïve adults, enrolled in the multicenter PHPT cohort in Thailand (NCT00433030) between January 1, 2000 and December 31, 2011, with no history of diabetes, who received exclusively and for at least 2 years tenofovir disoproxil fumarate (TDF), zidovudine (ZDV), stavudine (d4T) or didanosine + stavudine (ddI+d4T) as part of their first-line regimen. Diabetes was defined as confirmed either fasting plasma glucose ≥126 mg/dL or random glucose ≥200 mg/dL. Incidence of diabetes was estimated as the number of new cases divided by the total number of person-years. Cox proportional hazards models were used to compare the risk of diabetes between regimens.

Results: A total of 520 HIV-infected patients, 329 (63%) female, participated in this analysis. At ART initiation, median age was 34.1 years (interquartile range 29.5-40.1), body mass index (BMI) 20.7 kg/m^2 (18.9-22.9), CD4 count 139 cells/mm^3 (74-208) and HIV RNA load 4.8 log_{10} copies/mL (4.2-5.2). 329 (63%) patients received TDF, 28% ZDV, 7% d4T and 2% ddI+d4T, usually in addition to lamivudine or emtricitabine. Over 3,318 person-years, 13 patients met the criteria for diabetes. Incidence of new onset diabetes was 3.9 per 1,000 person-years (95% confidence interval [CI] 2.3-6.7). Upon multivariate analysis, adjusting for gender, age, BMI, hepatitis B surface antigen, hepatitis C antibody and CD4 cell count at ART initiation, the adjusted hazard ratios for new onset diabetes were 6.8 (95% CI 1.6-30.0) in patients on ZDV, 14.7 (1.3-167.8) on d4T, and 91.3 (12.4-674.2) on ddI+d4T compared to those on TDF containing regimens (reference) (p <0.001).

Conclusions: Overall, the incidence rate of diabetes in this lean and predominantly young, female population was relatively low. However, first-line use of ZDV, d4T and d4T+ddI resulted in increased diabetes incidence. In most ART programs, d4T as well as ddI have now been phased out but our study shows that ZDV as first-line regimen was associated with a higher risk of diabetes than TDF.

789 Diabetes Mellitus Among HIV-Infected Adults in Care in the United States, 2009–2010

Alfonso C. Hernandez-Romieu

Emory University Rollins School of Public Health, Decatur, GA, US

Background: Diabetes mellitus (DM) is increasingly prevalent among the U.S. general adult population, but prevalence estimates among HIV-infected persons, who are living longer, are lacking.

Methods: We used 2009-2010 data from the Medical Monitoring Project (MMP) to determine DM prevalence among a nationally representative cross-sectional sample of HIV-infected adults receiving medical care in the United States. Data were obtained through medical record abstraction and in-person interviews. Diagnosed DM was defined as a recorded diagnosis of DM or prescription of DM-specific pharmacotherapy; undiagnosed DM was defined as any record of fasting blood glucose ≥126 mg/dl or glycated hemoglobin ≥6.5% in the absence of diagnosed DM. Standardized prevalence ratios (sPR) were used to compare diagnosed DM prevalence among HIV-infected adults to the general U.S. population in the National Health and Nutrition Examination Survey 2009–2010. Bivariate analyses and multivariate logistic regression were used to examine factors associated with DM prevalence (diagnosed + undiagnosed) among HIV-infected adults.

Results: Overall, 14.2% (95% confidence interval [CI] 12.8-15.6) of HIV-infected adults had DM; 10.3% (CI 9.1-11.2) with diagnosed DM and 3.9% (CI 2.9-5.0) with undiagnosed DM. Compared to the U.S. adult population, the race-standardized prevalence of diagnosed DM among HIV-infected adults was substantially higher in those aged 20-44 years (sPR 2.27, CI 2.21-2.34), and lower in those aged 45-59 years (sPR 0.93, CI 0.92-0.94) and ≥60 years (sPR 0.78, CI 0.75-0.80). Among HIV-infected adults, factors independently associated with DM included older age, duration of HIV ≥10 years, and body mass index ≥ 30 kg/m^2 (Table 1).

Prevalence of and factors independently associated with diabetes mellitus among HIV-infected adults receiving medical care in the United States, Medical Monitoring Project, 2009-2010

	Sample (n)	Weighted Prevalence % (95% CI)	Adjusted Prevalence Ratio (95% CI) †	P
Total	8,655	14.2 (12.8, 15.6)		
Sex at birth				0.9
Male	6,333	13.5 (12.2, 14.9)*	ref.	
Female	2,322	16.1 (13.8, 18.4)	1.01 (0.88, 1.16)	
Race/ethnicity				0.2
White (non-Hispanic)	2,872	13.1 (10.7, 15.5)	ref.	
Black (non-Hispanic)	3,549	15.3 (13.6, 16.9)	1.15 (0.95, 1.39)	
Hispanic	1,831	13.8 (11.7, 15.9)	1.08 (0.87, 1.33)	
Other	403	14.4 (10.6, 18.2)	1.22 (0.95, 1.57)	
Age in years				<0.01
20-44	3,465	8.3 (7.1, 9.4)*	ref.	
45-60	4,351	17.0 (15.1, 19.0)	1.70 (1.48, 1.94)	
≥60	830	24.9 (21.5, 28.3)	2.53 (2.06, 3.12)	
Time since HIV diagnosis				<0.01
<5 years	1,897	8.2 (6.5, 10.0)*	ref.	
5-9 years	1,943	11.3 (9.9, 12.6)	1.20 (0.95, 1.50)	
≥10 years	4,808	17.9 (16.1, 19.6)	1.66 (1.37, 2.02)	
AIDS/Nadir CD4 count in cells/mm^3				0.4
AIDS or nadir CD4 0-199	5,965	15.2 (13.7, 16.8)*	1.11 (0.95, 1.30)	
No AIDS and nadir CD4 200-500	2,121	11.5 (9.4, 13.6)	ref.	
No AIDS and nadir CD4 >500	551	13.4 (9.8, 17.1)	1.14 (0.85, 1.54)	
Obesity (BMI≥30 kg/m^2)				<0.01
No	6,225	11.5 (9.9, 13.0)*	ref.	
Yes	2,081	22.3 (20.3, 24.4)	2.07 (1.77, 2.42)	
Positive Hepatitis C antibody				0.2
No	5,161	13.9 (12.5, 15.4)*	ref.	
Yes	1,374	18.4 (16.1, 20.7)	1.10 (0.95, 1.27)	

*P <0.05; †In addition to the variables presented in the table, the prevalence ratio is adjusted for education level, poverty, and geometric mean CD4 cell count during the 12 months prior to interview; weighted diabetes prevalence includes diagnosed and undiagnosed individuals; BMI = body mass index; CI = confidence interval

Conclusions: In the United States, one in seven HIV-infected adults has diagnosed or undiagnosed DM. Compared to the general population aged 20-44 years, same-aged HIV-infected adults are over twice as likely to have DM. Although obesity is a major risk factor for DM among HIV-infected adults, our data suggest that DM may be present at an earlier age in the context of HIV-infection and in the absence of traditional risk factors. Healthcare providers should implement recommended screening for DM to promote early interventions including lifestyle modifications for individuals with and at higher risk for DM.

790 Functional Vitamin D Deficiency With Initiation of Tenofovir-Based ART?

Evelyn Hsieh[1]; Liana Fraenkel[1]; Weibo Xia[2]; Yang Han[2]; Michael T Yin[3]; Karl Insogna[4]; Ting Zhu[2]; Taisheng Li[2]

[1]Yale University School of Medicine, New Haven, CT, US; [2]Peking Union Medical College Hospital, Beijing, China; [3]Columbia University Medical Center, New York, NY, US; [4]Yale University School of Medicine, New Haven, CT, US

Background: Antiretroviral regimens containing tenofovir disoproxil fumarate (TDF) have been associated with decreases in bone mineral density (BMD), and elevations in bone turnover markers (BTM) and intact parathyroid hormone (iPTH) in patients with HIV. Prior cross-sectional studies suggested that a functional vitamin D deficiency may in part explain these changes. To explore this hypothesis further, we measured change in plasma vitamin D binding protein (VDBP) levels from baseline to 48 weeks among a cohort of patients treated with TDF/lamivudine(3TC)/efavirenz(EFV) in the context of other serologic markers of vitamin D and bone metabolism.

Methods: We performed a secondary analysis using plasma samples collected at 0, 24, and 48 weeks after initiation of TDF/3TC/EFV from 140 adult participants enrolled in a multi-center randomized trial. Women over 45 years were excluded to avoid confounding due to menopausal status. Data regarding socio-demographic characteristics, BMI, $CD4^+$ counts, and HIV viral load were obtained as part of the parent study. Laboratory analyses included plasma VDBP, iPTH, total 25-hydroxyvitamin D (25OHD), the bone resorption marker collagen type 1 cross-linked C-telopeptide (CTX), and the bone formation marker total procollagen type 1 N-terminal propeptide (P1NP). Differences between time points were compared using the paired t-test.

Results: Our sample included 110 men and 30 women with a mean age of 33±9.6 yrs. Mean BMI remained stable from 0 to 48 wks (21.7±3.0 v. 22.0±3.2 kg/m^2, p=0.20), however mean $CD4^+$ count increased significantly (279.5±117.1 v. 424.6±176.9 cells/mm^3, p<0.001) and median viral load decreased from 53767 (IQR: 19802 to 136493) to 0 (IQR:0 to 10) copies/mL. Significant increases were observed in VDBP levels from 0 to 24 wks followed by smaller increases from 24 to 48 wks (see Table 1). Similar increases were detected in iPTH levels, however 25OHD levels remained relatively stable. BTM levels increased significantly from 0 to 24 wks followed by a slight decline (CTX) or stabilization (P1NP), however remained significantly higher compared with baseline at 48 wks.

Markers of Vitamin D and Bone Metabolism at 0, 24 and 48 Weeks after Initiation of Tenofovir/ Lamivudine/Efavirenz (N=140)

	0 weeks (Mean±SD)	24 weeks (Mean±SD)	48 weeks (Mean±SD)	p 0 to 24 wks	p 24 to 48 wks	p 0 to 48 wks
VDBP *mg/mL*	177.8±102.5	216.4±134.1	236.1±145.9	<0.001	0.002	<0.001
iPTH *pg/mL*	34.4±12.8	43.2±16.9	49.4±19.4	<0.001	0.001	<0.001
25OHD *ng/mL*	25.4±10.5	26.9±11.9	25.8±10.3	0.03	0.13	0.48
CTX *ng/mL*	0.29±0.16	0.47±0.18	0.41±0.16	<0.001	<0.001	<0.001
P1NP *ng/mL*	43.9±18.9	66.1±22.2	67.6±22.2	<0.001	0.32	<0.001

Conclusions: Plasma levels of VDBP rose significantly in the first 24 wks after initiation of TDF/3TC/EFV, followed by a more modest increase from 24 to 48 wks. This change was observed in concert with elevations iPTH and BTMs, despite stable 25OHD levels, supporting a potential mechanistic role for VDBP in bone loss associated with TDF therapy.

791 Determinants of Parathyroid Hormone Levels in HIV-positive Tenofovir-treated Patients with Normal Renal Function

Letizia Marinaro; Andrea Calcagno; Jessica Cusato; Elisabetta Scarvaglieri; Marco Simiele; Maria Cristina Tettoni; Laura Trentini; Antonio D'Avolio; Giovanni Di Perri; Stefano Bonora
Unit of Infectious Diseases, Turin, Italy

Background: Secondary hyperparathyroidism may develop in HIV-positive patients in case of vitamin D deficiency and calcium or phosphorus metabolism disorders. Traditional (age, gender, BMI) and therapeutic determinants [tenofovir (TDF) exposure] have been described but the role of TDF exposure as well as of genetic polymorphisms in key genes is currently unknown.

Methods: Adult HIV-positive patients on TDF-containing HAARTs since at least six months, presenting estimated creatinine clearance (eCRCL) above 60 ml/min, with no significant comorbidity (hypertension, diabetes, urinary tract abnormalities), signing an informed consent were included. Twelve-hours TDF plasma (pC_{12}) and urinary concentration (uC_{12}) were measured through validated HPLC/MS-MS method. Results are expressed as medians (IQR); non parametric tests were used for all analysis. Single Nucleotide Polymorphisms (SNPs) in the following genes were obtained through real-time PCR: *ABCB1, ABCC2, ABCC4, ABCC10, SLC22A6, SLC28A2, CYP27B1, CYP24A1, VDR.*

Results: 294 patients (75.2% male, 84.4% Caucasian) were enrolled. Age, BMI and eCRCL were 46 years (39.7-52), 23.7 kg/m^2 (22-26.5) and 91.6 ml/min (79.5-107) respectively. Median CD4 were 552 cell/uL (409-713) and 278 patients (94.6%) presented a plasma viral load <50 copies/mL after 55.2 months (27.8-88) of TDF intake. Vitamin D, parathyroid hormone (PTH) and phosphorus were 21.2 ng/dL (13.8-31.3), 52.2 pg/mL (40-66.4) and 3 mg/dL (2.7-3.4) with respectively 72.3%, 15% and 16.8% of patients presenting vitamin D deficiency (<30 ng/mL), secondary hyperparathyroidism (>79.6 pg/mL) and hypophosphoremia (<2.6 mg/dL). At multivariate linear regression (including also age, gender, BMI and time on TDF) vitamin D levels (p>0.001), cirrhosis (p=0.04) and the vitamin D receptor uncommon variants Cdx2 (rs11568820, p=0.025) were independent predictors of PTH. At multivariate linear regression PTH levels (p=0.023), HAART class (NNRTIs associated with the lowest levels, p=0.005), SLC28A2 124 (rs11854484, p=0.037) SNP and TDF urinary output (urinary TDF/plasma TDF, p=0.038) were independent predictors of phosphorus levels.

Conclusions: A significant proportion of patients on long-term TDF-based treatment showed vitamin D deficiency and secondary hyperparathyroidism: the latter is more common in cirrhotic patients and in patients with non-functional vitamin D receptor. Genetic and pharmacokinetic markers can be used to identify patients at higher risk of hypophosphatemia and bone metabolism dysfunction.

THURSDAY, FEBRUARY 26, 2015

Session P-Q8 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Renal Dysfunction: ART and Biomarkers

792 Elevated Tenofovir Exposure via Intensive PK Monitoring Is Associated With Progressive Kidney Function Decline

Sanjiv M. Baxi[1]; Rebecca Scherzer[1]; Ruth M. Greenblatt[1]; Howard Minkoff[2]; Kathryn Anastos[5]; Mardge H. Cohen[4]; Mary A. Young[3]; Monica Gandhi[1]; Michael G. Shlipak[1]
[1]*University of California San Francisco, San Francisco, CA, US;* [2]*State University of New York Downstate Medical Center, Brooklyn, NY, US;* [3]*Georgetown University, Washington, DC, US;* [4]*John Stroger (formerly Cook County) Hospital, Chicago, IL, US;* [5]*Montefiore Medical Center, University Hospital for Albert Einstein College of Medicine, Bronx, NY, US*

Background: Tenofovir disoproxil fumarate (TDF) is commonly used for HIV treatment, but risk factors for tenofovir (TFV)-associated kidney disease are relatively understudied. Among a diverse cohort of HIV-infected women on TFV-based therapy, we performed intensive pharmacokinetic (PK) studies to measure TFV exposure and assess its association with subsequent kidney function.

Methods: The Women's Interagency HIV Study (WIHS) is a multicenter, prospective cohort of representative HIV-infected women. Participants on TFV-based therapy (n=105) underwent 24-hour intensive PK sampling after witnessed dose under routine-use, steady-state conditions. Serial creatinine measures allowed assessment of kidney function (estimated GFR [eGFR] by the CKD-EPI collaboration equation) over the succeeding 7 years in all participants. Multivariable linear mixed models were used to evaluate the relationship between TFV area-under-the-time-concentration-curves (AUCs) at baseline with subsequent kidney function. Additional covariates adjusted for in the models include baseline age, baseline diabetes and hypertension, race, body mass index (BMI), ritonavir (RTV) use, duration of prior TFV exposure, CD4 cell count and viral load.

Results: The mean age of 105 participants was 43 (range 39-65) years; 63% were African-American, 25% Hispanic and 12% white. Baseline BMI was weakly positively correlated with eGFR (ρ=0.22, p=0.019) and negatively with TFV AUC (ρ=0.24, p=0.012). The figure shows the trajectory of eGFR over time by tertile of TFV AUC. The eGFR was significantly lower at baseline in the highest compared with lowest tertiles (mean ± SE) of TFV AUC (80 ± 4.3 vs. 104 ± 2.5 ml/min, p<.0001). By year 7, this difference had widened (72.4 ± 4.9 vs. 104.9 ± 2.9, p<.0001). After multivariable adjustment with baseline variables, the highest tertile of TFV AUC remained associated with significantly lower eGFR relative to the lowest tertile at both baseline (-15, 95% CI: -25 to -5, p=0.0047) and year 7 (-23, 95% CI: -34 to -12, p=0.0002). The association of TFV AUC with eGFR did not differ by BMI, concomitant use of RTV or age (tests for interaction p>0.1).

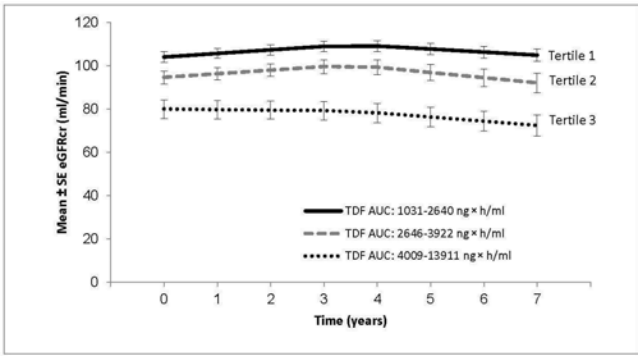


Figure. Association of baseline tenofovir area-under-the-time-concentration-curves tertile with estimated glomerular filtration trajectory in 105 HIV-infected women.

Conclusions: In this diverse group of women undergoing intensive TFV PK sampling, we found a strong and significant association between higher TFV exposure over time and faster declines in subsequent kidney function longitudinally. Variations in tenofovir drug exposure, although rarely assessed, may partially account for subsequent nephrotoxicity in HIV-infected patients.

793 Impact of TDF+PI/r on Renal Function in Sub-Saharan Africa : 2LADY/ANRS 12169 Trial

Arsene Hema[1]; **Amandine Cournil**[2]; Laura Ciaffi[2]; Sabrina Eymard-Duvernay[2]; Assane Diouf[3]; Nestor Manga[4]; Vincent Le Moing[2]; Jacques Reynes[2]; Sinata Koulla-Shiro[5]; Eric Delaporte[2]

[1]CHU Souro Sanou, Bobo Dioulasso, Burkina Faso; [2]IRD/UM 1, Montpellier, France; [3]Le Centre Régional de Recherche et de Formation à la Prise en Charge Clinique de Fann, Dakar, Senegal; [4]Yaounde Military Hospital, Yaounde, Cameroon; [5]FMSB/University Yaounde 1, Yaounde, Cameroon

Background: A strong genetic susceptibility to chronic kidney disease (CKD) has been observed in sub-Saharan African populations. The current WHO-recommended second line antiretroviral treatment (ART) associates a protease inhibitor boosted with ritonavir (PI/r) in combination with Tenofovir Disoproxil Fumarate (TDF) or Zidovudine (AZT) + lamivudine or emtricitabine (FTC). TDF + PI/r has been associated with proximal tubular dysfunction and CKD.

The aim was to determine if TDF+PI/r use was associated with changes in renal function in HIV patients starting a second line ART in comparison with a regimen without TDF (abacavir (ABC) + didanosine (ddI) + LPV/r) in three African countries (Cameroun, Senegal and Burkina Faso).

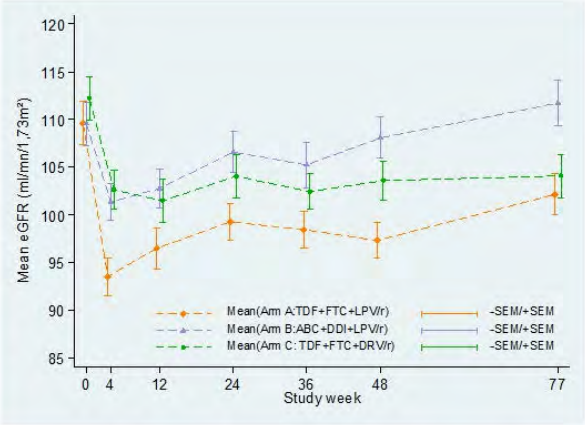
Methods: HIV-1 positive adults, failing standard first line ART were randomized to either A: TDF+FTC+LPV/r; B: ABC + ddI + LPV/r or C: TDF + FTC + darunavir (DRV) /r and followed until 18 months. Patients with an MDRD-estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1,73m^2 were included in this analysis.

We compared levels and changes in eGFR using multivariable linear regressions. First occurrence of CKD (eGFR<60ml/ml/1,73m^2) was compared using Mantel-Haenszel tests.

Results: Out of 454 randomized patients, 443 were included in this analysis. Mean age was 39 years (SD: 9.7) and 72% were women. Thirty-nine patients (9%) had hypertension and 2 (0.4%) diabetes. Median follow-up was 16 months.

The rate of decline of eGFR from baseline to week 4 was marked in all treatment groups with a greater mean decrease in TDF+FTC+LPV/r arm (-16.6 ml/min/1.73m^2) than in ABC+DDI+LPV/r arm

(-8.2; P=10^{-3}); and TDF+FTC+DRV/r arm (-9.6; P=10^{-3}). From week 4 to month 18, mean eGFR remained stable in TDF+FTC+DRV/r and increased in the other two arms. The greatest increase was observed in ABC+DDI+LPV/r (+10.4). At month 18, mean eGFR in the non-TDF containing regimen (112.3) recovered its baseline level and was significantly greater than eGFR 18-month-levels in the TDF-containing regimens (with LPV/r; 100.8; P=5.10^{-3}; with DRV/r; 104.9; P=0.02). Incidence of CKD was 5%; 5% and 4% person-year in arms A, B and C, respectively and did not differ by treatment arms (P=0.78).



eGFR changes by treatment arm

Conclusions: Randomization to TDF+IP/r was associated with a mild non progressive decrease of eGFR after 18 months in patients with eGFR>60ml/ml/1,73m^2 at baseline. These results suggest a good renal tolerance of the second line associating TDF+FTC+IP/r in patients in sub-Saharan Africa.

794 Renal Tubular Disease and the Relationship With Tenofovir and Atazanavir Exposure

Lisa Hamzah[1]; John Booth[2]; Catherine Horsfield[3]; Rachael Jones[4]; Jeremy Levy[5]; Deborah Williams[6]; Nadia Khatib[7]; Rachel Hilton[3]; John Connolly[2]; Frank A. Post[8]

[1]King's College London, London, United Kingdom; [2]University College London, London, United Kingdom; [3]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [4]Chelsea and Westminster Hospital, NHS Foundation Trust, London, United Kingdom; [5]Imperial College London, London, United Kingdom; [6]Brighton and Sussex Hospitals NHS Trust, London, United Kingdom; [7]Heart of England NHS Foundation Trust, Birmingham, United Kingdom; [8]King's College Hospital NHS Foundation Trust, London, United Kingdom

Background: Renal tubular dysfunction is common in HIV+ patients treated with antiretroviral therapy (ART). The pathological spectrum of renal tubular disease (RTD) and its association with ART remains poorly described.

Methods: We reviewed 265 consecutive renal biopsies (2000-2012) of HIV+ patients attending 8 clinics in the UK. We describe the clinical characteristics of patients with RTD and compared current/recent exposure (at the time of, or up to 3 months prior to the date of biopsy) to potentially nephrotoxic ART (tenofovir [TDF], atazanavir [ATV], indinavir [IDV] and lopinavir [LPV]) in 54 RTD cases and 64 patients with immune complex kidney disease (ICKD). Kruskall-Wallis, Chi squared, Fisher's exact tests and Mantel-Haenszel methods were used to evaluate between group differences and calculate odds ratios (OR).

Results: RTD could be classified into 3 distinct patterns: acute tubular injury (ATI, n=22), tubulointerstitial nephritis (TIN, n=20) and interstitial fibrosis and tubular atrophy (IFTA, n=12). Compared with TIN and IFTA, ATI cases were less likely to be of black ethnicity (10 vs. 55 and 42%, p=0.006) and more likely to be on ART (100 vs. 55 and 68%, p=0.001) with HIV RNA <200 copies/mL (100 vs. 54 and 58%, p<0.001) at biopsy. There were no significant differences between other HIV and renal parameters in patients with ATI, TIN and IFTA, including median time since HIV diagnosis (11, 4 and 13 years), CD4 nadir (154, 102 and 87 cells/mm^3), current CD4 count (364, 262 and 227 cells/mm^3), eGFR (47, 25 and 42 mL/min/1.73m^2) and proteinuria (1.4, 1.8 and 1.2 g/24h). 5 ATI cases had biochemical evidence of proximal tubulopathy/Fanconi syndrome vs. none with TIN or IFTA. With resolution, renal function returned to baseline in 77, 50 and 58% of subjects. Compared with ICKD cases, patients with ATI were more likely to have current/recent exposure to TDF (OR [95% CI] 9.8 [2.6, 36.7]), p<0.001), ATV (OR 7.8 [1.2, 50.2]), p=0.01) or LPV (OR 3.3 [1.0, 10.9], p=0.04). No consistent ART associations were observed with TIN or IFTA.

Conclusions: RTD was present in 20% of renal biopsies and comprised three distinct pathological injury patterns with considerable clinical overlap. Of these, ATI was strongly associated with TDF and ATV exposure.

795 Safety of Tenofovir Alafenamide in Renal Impairment

Anton Pozniak[2]; Jose R Arribas[3]; Samir K. Gupta[4]; Frank A. Post[5]; Anchalee Avihingsanon[6]; Gordon Crofoot[7]; Kenneth A. Lichtenstein[8]; Moti Ramgopal[9]; Ploenchan Chetchotisakd[10]; **Marshall W. Fordyce**[1]

[1]Gilead Sciences Inc, Foster City, CA, US; [2]Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom; [3]Hospital Universitario La Paz, Madrid, Spain; [4]Indiana University School of Medicine, Indianapolis, IN, US; [5]King's College Hospital NHS Foundation Trust, London, United Kingdom; [6]HIV-NAT, Thai Red Cross AIDS Research Center and Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [7]Crofoot Research, Houston, TX, US; [8]National Jewish Health, Denver, CO, US; [9]Midway Research Center, Ft. Pierce, FL, US; [10]Khon Kaen University, Khon Kaen, Thailand

Background: Tenofovir (TFV) is renally eliminated, and the prodrug, tenofovir disoproxil fumarate (TDF), has been associated with renal toxicity and reduced bone mineral density (BMD), and must be dose adjusted in patients with estimated glomerular filtration rate (eGFR) < 50mL/min. Tenofovir alafenamide (TAF) is a novel prodrug of TFV that is not renally eliminated and at clinical doses results in 90% lower plasma TFV levels as compared to TDF. The safety and efficacy of a once-daily single tablet regimen of elvitegravir, cobicistat, emtricitabine, and TAF (E/C/F/TAF) was assessed in HIV-1 infected patients with mild to moderate renal impairment.

Methods: Virologically suppressed adults with stable $eGFR_{CG}$ (CockroftGault) of 30 to 69 mL/min had their treatment switched from both TDF- and non-TDF-containing regimens to open-label E/C/F/TAF. Week 24 efficacy and safety data are described, including tests of renal function and BMD. Actual GFR (aGFR) was assessed with iohexol clearance in a subset of subjects.

Results: Of 242 subjects enrolled and dosed, mean age was 58 years (range: 24 – 82), 18% Black, 39% hypertension, and 14% diabetes. 65% were taking TDF-containing regimens prior to switch. At baseline, median $eGFR_{C-G}$ was 55.6 mL/min (33% $eGFR_{C-G}$ 30-49 mL/min). 95% of subjects maintained HIV-1 VL <50 c/mL at Week 24 (FDA Snapshot). At Week 24, the median (Q1, Q3) change from baseline $eGFR_{C-G}$ was -0.4 (-4.7, 4.5) mL/min, eGFR-cystatin C 3.8 (-4.8, 11.2) mL/min/1.73m2, and aGFR (n=32, 68.8% TDF at baseline) was 0.1 (-4.3, 4.4) mL/min, indicating that GFR was not affected by E/C/F/TAF. Two subjects (0.8%) discontinued study drug for decreased GFR by $eGFR_{C-G}$ and eGFR-cystatin C, neither with evidence of renal tubulopathy. The prevalence of clinically significant proteinuria (UPCR > 200 mg/g) and albuminuria (UACR ≥ 30 mg/g) decreased from 42% to 21% and 49% to 27%, respectively. Significant decreases in urine retinol binding protein to creatinine ratio, beta2microglobulin to creatinine ratio, and fractional excretion of uric acid were observed (p<0.001 for all). Hip and spine BMD percentage change from baseline to Week 24 was 0.74% (-0.71, 2.03) and 1.27% (-0.44, 3.83) (median, IQR), respectively.

Conclusions: These 24 week data support the virologic efficacy and renal and bone safety of once daily single-tablet E/C/F/TAF for use in HIV+ patients with mild and moderate renal impairment (eGFR 30 to 69 mL/min). Switch to E/C/F/TAF was associated with no change in aGFR and with reductions in proteinuria.

796 Elevated Nonclassical Monocytes and Urine Fibrotic Markers in HIV Albuminuria

Brooks I. Mitchell; Mary Margeret Byron; Roland C. Ng; Dominic C. Chow; Pichaya O-charoen; Lishomwa C. Ndhlovu; Cecilia M. Shikuma

University of Hawaii, Honolulu, HI, US

Background: Presence of albuminuria (ALB) predicts an accelerated loss in renal function. Rates of ALB are high among HIV-infected individuals on antiretroviral therapy (ART). We investigated the relationship of monocyte (MO) subsets and urine inflammatory and fibrotic markers to ALB in stable HIV-infected subjects on ART.

Methods: Cross-sectional analyses on Hawaii Aging with HIV-CVD cohort subjects ≥ 40 years old and on ART ≥ 6 months. MO subsets (classical, intermediate, non-classical) were determined in banked peripheral blood mononuclear cells (PBMC) using multi-parametric flow cytometry. Entry random urine samples were assessed for albumin/creatinine ratios (ACR). Urine samples were measured for inflammatory (IP-10, MCP-1, and IL-18) and fibrotic (TGF-β_1, TGF-β_2, TGF-β_3, collagen IV, and TIMP-1) markers using Luminex technology. Statistical analyses performed were Wilcoxon Rank and chi-squared tests, Pearson correlations, and multivariable linear regressions.

Results: Among 96 HIV-infected subjects with measured ACR (87% male, 59% Caucasian, and 89% undetectable HIV RNA with median CD4 of 495.5 cells/μL), 18 patients (19%) had ALB [89% with moderate ALB (ACR 30-300 mg/g) and 11% with severe ALB (ACR > 300 mg/g)]. Subjects with ALB were older (median age 57 vs. 50, p=0.013), and had higher rates of hypertension (67% vs. 31%, p=0.010) and use of ACE inhibitors and/or ARBs (50% vs. 15%, p=0.004); but did not differ in rates of diabetes (10%) or use of Tenofovir (77%) or Ritonavir (38%). Only non-classical ($CD14^{low/+}CD16^{+}$) MO subset was significantly elevated in subjects with ALB ($2.68x10^7$ cells/μL vs. $1.96x10^7$ cells/μL, p=0.034) and was correlated to ACR (r=0.238, p=0.019). Non-classical MO subset, but not other subsets, was a significant predictor of ALB independent of hypertension, BMI, and total cholesterol/HDL ratio (β=0.223, p=0.021). In 37 subjects assessed for urinary biomarkers, only urine TGF-β_1 and collagen IV had significantly higher average net MFI in albuminuric compared to non-albuminuric subjects (TGF-β_1; 14.4 vs. 3.5, p=0.039 and collagen IV; 1160.9 vs. 702.0, p=0.042). Levels of urine TGF-β_1 showed a significant correlation with ACR (r=0.336, p=0.042) and non-classical MO subset (r=0.464, p=0.017).

Conclusions: ALB in HIV-infected individuals on ART is associated with elevated levels of non-classical MO and urine pro-fibrotic factors. Alterations in MO subsets and pro-fibrotic factors may play a important role in kidney injury during chronic HIV infection.

797 Kidney Dysfunction and Markers of Inflammation in the Multicenter AIDS Cohort Study

Alison G. Abraham[1]; Annie Darilay[2]; Heather McKay[1]; Joseph B. Margolick[1]; Michelle M. Estrella[3]; Frank J. Palella[4]; Robert Bolan[5]; Charles R. Rinaldo[6]; Lisa P. Jacobson[1]

[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [2]AstraZeneca, Gaithersburg, MD, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [5]Los Angeles LGBT Center, Los Angeles, CA, US; [6]University of Pittsburgh, Pittsburgh, PA, US

Background: HIV-associated chronic immune activation and inflammation may contribute to increased risk for kidney disease among HIV-infected (HIV+) individuals, even after viral suppression. We examined associations between inflammatory processes and kidney function in treated and virally suppressed HIV+ and HIV– men from the Multicenter AIDS Cohort Study.

Methods: Glomerular filtration rate (GFR) was directly measured using decay of plasma iohexol concentration. Twelve markers of inflammation were measured from stored blood samples (C-Reactive Protein, Soluble TNF-receptor 2, Soluble Interleukin (IL) 2-receptor-α, Soluble GP130, Soluble CD27, Monocyte Chemoattractant Protein-1, Interferon γ-Induced Protein 10, TNF-α, IL-6, Soluble CD14, IL-8, IL-10). Exploratory factor analysis (EFA) was used to identify underlying inflammatory processes, and factors were validated in an independent dataset. The validated factor scores were used in adjusted logistic regression analyses to evaluate their associations with kidney outcomes: reduced GFR (GFR≤90 ml/min/1.73m^2); hyperfiltration (GFR >140 ml/min/1.73m^2 - 1 ml/min/1.73m^2 for each year over age 40); and urine protein:creatinine ratio (uPCr) category (≤100, 100-200, >200 mg/g).

Results: 434 HIV+ men, all on antiretroviral therapy and 80% virally suppressed, and 200 HIV- men had available GFR determinations and inflammatory biomarker levels. HIV+ men had higher levels of cystatin C (median: 0.79 versus 0.75 mg/dl) and uPCr (median: 98 versus 66 mg/g). From the EFA, three factors were retained that accounted for 60% of the total variance in inflammatory marker levels; only the first two factors could be replicated in a validation set. Factor 1 (dominated by markers: sTNF receptor 2, sIL 2-receptor-α, sGP130, sCD27, and sCD14) scores (shown in the Figure) were significantly (p<0.05) related to a greater odds of GFR≤90 ml/min/1.73m^2 (OR=2.0), a greater odds of uPCr >200 mg/g (OR=2.2), and a lower odds of hyperfiltration (OR=0.5), as well as with a history of diabetes (OR=1.6) and a history of hypertension (OR=1.3). Levels of all of these markers except GP130 were significantly higher in HIV+ men. Factor 2 (dominated by markers: IL-6, IL-8 and TNF-α) was not significantly associated with any kidney outcomes.

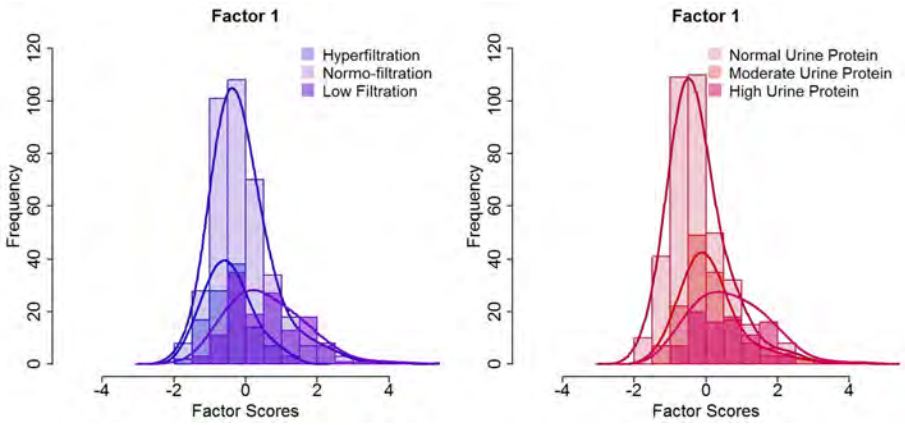


Figure. Distribution of Factor 1 scores across categories of GFR and urine protein:creatinine ratio outcomes.

Conclusions: Higher circulating levels of immune activation markers among treated HIV+ individuals, despite virologic suppression, may partially explain their higher burden of kidney dysfunction compared to HIV- persons.

THURSDAY, FEBRUARY 26, 2015

Session P-Q9 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Renal Transplantation: Long-Term Outcomes

798 Risk Factors for Acute Allograft Rejection in HIV Positive Kidney Transplant Recipients

Esther N. Gathogo[1]; Mark Harber[2]; Sanjay R. Bhagani[2]; Joanne Baxter[3]; Vincent Lee[4]; Jeremy Levy[5]; Rachael Jones[6]; Rachel Hilton[7]; Graham Davies[1]; Frank A. Post[1]

[1]King's College London, London, United Kingdom; [2]Royal Free London NHS Foundation Trust, London, United Kingdom; [3]North Manchester General Hospital, Manchester, United Kingdom; [4]Central Manchester University Hospitals, Manchester, United Kingdom; [5]Imperial College Healthcare NHS Trust, London, United Kingdom; [6]Chelsea and Westminster Hospital, NHS Foundation Trust, London, United Kingdom; [7]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

Background: Kidney transplantation (KT) of HIV positive patients has transformed the management of end-stage kidney disease in this population. Although favourable outcomes have been reported, patients experience high rates of acute allograft rejection (AR). We examined factors associated with AR in the first year post-KT, with particular emphasis on the choice of calcineurin inhibitor (CNI) immunosuppressive therapy.

Methods: We conducted a national observational cohort study of HIV/KT in the UK. Patients were included if HIV positive at KT, transplanted in the UK between 01/2005 and 12/2013, and did not experience primary graft failure. Kaplan-Meier methods were used to estimate host/graft survival and cumulative incidence of biopsy proven AR. Logrank tests were used to compare survival, and Cox proportional hazard models to examine factors associated with AR.

Results: Seventy-seven (91%) of 85 HIV+ kidney transplant recipients were included in the analyses. The mean age was 44.8 years, 75% black ethnicity, median CD4 cell count 277 cells/mm^3, 97% had HIV RNA <200 c/mL. 32 participants initiated ciclosporin (CsA) and 45 Tacrolimus (Tac) based immunosuppression. The overall one-year patient and graft survival were 97.3% and 94.6% respectively. AR was observed in 28 patients (36%), with a median time from KT to AR of 2.6 (IQR 0.5, 5.9) months. The cumulative incidence of AR at 1 year was 57% and 20% among patients who started CsA and Tac respectively (p=0.002). The only factor that was significantly associated with AR was choice of CNI (HR for Tac vs, CsA 0.30 [95% CI 0.13, 0.67], p=0.003). Recipient age, gender, ethnicity, deceased donor graft, year of KT, nadir or current CD4 cell count and viral hepatitis status were not associated with AR. In a sensitivity analysis which excluded 8 patients with AR in the first two weeks post KT, use of Tac (HR 0.17 [0.06, 0.48]), abacavir (0.40 [0.17, 0.96]) and protease inhibitors (2.56 [1.04, 6.27]) were associated with AR in univariable analysis; only use of Tac (HR 0.26 [0.07, 0.94]) associated with AR in multivariable analysis. Use of Tac was generally safe with one patient each developing CNI toxicity with CsA and Tac.

Conclusions: The use of Tac was associated with a significantly reduced incidence of AR in the first year post KT. Our data suggest that Tac is the preferred CNI in the context of HIV infection. Use of protease inhibitor-sparing antiretroviral therapy may facilitate the safe administration of Tac.

799 Survival in HIV-Positive Transplant Recipients Compared to Matched Registry Controls

Michelle E. Roland[1]; Burc Barin[2]; Shirish Huprikar[3]; **Michael Wong**[4]; Emily Blumberg[5]; David Simon[6]; Margaret Ragni[7]; Don Stablein[2]; Peter Stock[1]
HIV-TR Study Team

[1]University of California San Francisco, San Francisco, CA, US; [2]EMMES Corporation, Rockville, MD, US; [3]Mount Sinai School of Medicine, New York, NY, US; [4]Beth Israel Deaconess Medical Center, Boston, MA, US; [5]University of Pennsylvania, Philadephia, PA, US; [6]Rush University Medical Center, Chicago, IL, US; [7]University of Pittsburgh, Pittsburgh, PA, US

Background: We designed a 21-center study to test the hypothesis that immunosuppression does not accelerate HIV disease progression in transplant recipients with relatively intact immune systems and suppressed viremia. We further hypothesized that HIV+ patients would be higher risk but acceptable transplant candidates, similar to other higher risk groups. We previously described 3-year outcomes in 150 kidney (KTR) and 125 liver recipients (LTR). We now describe 5-year outcomes compared with HIV-negative controls.

Methods: We examined time to graft failure, death-censored graft failure, and death. Controls were identified from Scientific Registry of Transplant Recipients (SRTR). We fit 4 proportional hazards (PH) regression models: risk-matched and demographic-matched models examining HIV status, a demographic-matched model adjusting for risk score, and an unmatched model. We calculated case risk scores from a PH model adjusting for predictors among SRTR controls, identifying 4 controls per case after ranking by risk score. We created demographic-matched sets from randomly selected controls matched for age, gender, race, donor type, and time of transplant.

Results: In KTR, risk-matched and unmatched analyses indicated a marginally significant hazard ratio (HR) for graft loss (HR 1.4 [p=0.052] and 1.3 [p=0.07]), but no significant increase in risk of other events among HIV-positive KTR. All models demonstrated a statistically significantly higher relative hazard of graft loss or death (except risk-matched and

death) in HIV-positive LTR. The absolute difference in the proportion of deaths was 6.7% in the risk-matched control analysis. HIV status was not significant in death-censored graft failure models.

Table 1 Survival in HIV-Positive Transplant Recipients Compared to Matched Registry Controls

A. Graft failure and death among HIV-infected transplant recipients and the uninfected control groups

	Number of Events (%)		
	Graft Failure	Graft Failure (death censored)	Death
Kidney Recipients			
HIV-TR Cases (N=150)	46 (30.7%)	31 (20.7%)	17 (11.3%)
Risk Match Controls* (N=600)	162 (27.0%)	119 (20.0%)	71 (11.8%)
Demographic Controls (N=600)	174 (29.0%)	114 (19%)	76 (12.7%)
Unmatched Controls (N=85153)	20757 (24.4%)	11982 (14.1%)	10933 (12.8%)
Liver Recipients			
HIV-TR Cases (N=124)	57 (46.0%)	23 (18.6%)	45 (36.3%)
Risk Match Controls* (N=496)	161 (32.5%)	82 (16.5%)	147 (29.6%)
Demographic Controls (N=496)	170 (34.3%)	81 (16.3%)	133 (26.8%)
Unmatched Controls (N=32399)	10342 (31.9%)	4281 (13.2%)	8475 (26.2%)

*For each endpoint, separate risk models were used to identify the three risk match control groups.

B. Proportional Hazards Regression Results for HIV Status by Outcome and Match Model: Kidney Transplant Recipients

Outcome	Model	Hazard Ratio (95% CI)	P Value
Graft Failure	Risk Score Match	1.418 (0.997-2.017)	0.05
	Demographic Match Adjusted for Risk Score	1.115 (0.780-1.593)	0.55
	Demographic Match	1.081 (0.759-1.540)	0.67
	Unmatched, Adjusted for covariates	1.311 (0.974-1.765)	0.07
Graft Failure (Death Censored)	Risk Score Match	1.096 (0.495-2.426)	0.82
	Demographic Match Adjusted for Risk Score	1.077 (0.700-1.658)	0.74
	Demographic Match	1.099 (0.715-1.687)	0.67
	Unmatched, Adjusted for covariates	1.305 (0.910-1.871)	0.15
Death	Risk Score Match	1.172 (0.669-2.055)	0.58
	Demographic Match Adjusted for Risk Score	1.089 (0.617-1.920)	0.77
	Demographic Match	0.995 (0.574-1.725)	0.99
	Unmatched, Adjusted for covariates	1.145 (0.700-1.873)	0.59

C. Proportional Hazards Regression Results for HIV Status by Outcome and Match Model: Liver Transplant Recipients

Outcome	Model	Hazard Ratio (95% CI)	P Value
Graft Failure	Risk Score Match	1.530 (1.106-2.115)	0.01
	Demographic Match Adjusted for Risk Score	1.607 (1.159-2.227)	0.004
	Demographic Match	1.601 (1.161-2.209)	0.004
	Unmatched, Adjusted for covariates	1.518 (1.167-1.974)	0.002
Graft Failure (Death Censored)	Risk Score Match	1.389 (0.847-2.278)	0.19
	Demographic Match Adjusted for Risk Score	1.253 (0.755-2.080)	0.38
	Demographic Match	1.335 (0.820-2.175)	0.25
	Unmatched, Adjusted for covariates	1.238 (0.819-1.872)	0.31
Death	Risk Score Match	1.354 (0.941-1.949)	0.10
	Demographic Match Adjusted for Risk Score	1.644 (1.134-2.381)	0.01
	Demographic Match	1.612 (1.120-2.321)	0.01
	Unmatched, Adjusted for covariates	1.518 (1.129-2.040)	0.01

Conclusions: In the risk-, demographic- and unmatched analyses, HIV-negative KTR had outcomes that were not statistically different compared with controls, suggesting that renal transplantation should be standard of care for HIV-positive patients with end stage renal disease. The increased risk for HIV-positive liver recipients was modest, supporting transplant among this higher risk population as a viable option. Patient selection should be informed by prior analyses identifying low BMI, dual liver-kidney transplant, and HCV co-infection as factors associated with poor outcome. However, the availability of interferon-free regimens and direct acting antivirals are anticipated to improve transplant outcomes among LTR with HIV-HCV co-infection.

THURSDAY, FEBRUARY 26, 2015

Session P-Q10 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Pulmonary Disease

800 Risk Factors for Airflow Obstruction Among HIV+ Individuals in Nairobi, Kenya

Engi F. Attia[1]; Elizabeth Maleche-Obimbo[2]; Nelly Yatich[1]; Lillian Ndukwe[3]; Julia Njoroge[3]; Sameh Sakr[3]; Neveen El Antouny[3]; Fr. Mena Attwa[3]; Kristina Crothers[1]; Michael Chung[1]

[1]University of Washington, Seattle, WA, US; [2]University of Nairobi, Nairobi, Kenya; [3]Coptic Hope Center for Infectious Diseases, Nairobi, Kenya

Background: Antiretroviral therapy (ART) and prolonged survival are shifting the spectrum of HIV-related pulmonary complications toward a greater burden of chronic lung disease (CLD). In developing countries, this impacts HIV+ individuals at all ages, including adolescent survivors of vertically-acquired HIV, yet risk factors for CLD are incompletely understood. We hypothesized that vertically-acquired HIV, indoor biofuel burning and cigarette smoking are associated with airflow obstruction, a CLD manifestation, among HIV+ individuals in Nairobi.

Methods: We performed a cross-sectional analysis of 451 HIV+ adults and adolescents ≥10 years old enrolled in the Coptic Hope Center for Infectious Diseases in Nairobi; HIV acquisition route was assessed at enrolment. Included adolescents met criteria for vertically-acquired HIV. Subjects underwent pre- and post-bronchodilator (BD) spirometry per American Thoracic Society standards. Oxygen saturation was measured before and after ambulation. Respiratory symptoms, biofuel burning, smoking and other exposures were gathered via questionnaires. Recent CD4 was abstracted from Hope Center databases. We generated multivariable logistic regression models to determine the independent risk of vertically-acquired HIV, indoor biofuel burning and cigarette smoking with airflow obstruction, defined as the post-BD ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1/FVC) <0.7.

Results: Recent CD4 was significantly higher among adolescents though most subjects were on ART (Table). No adolescents reported cigarette smoking. Biofuel burning did not differ by age. Adolescents had twice the prevalence of cough, phlegm and desaturation and were more likely to have airflow obstruction. In multivariable analyses, vertically-acquired HIV (OR 2.84, *95% CI* 1.12-7.20) and cigarette smoking (OR 3.11, *95% CI* 1.23-7.86) were significantly associated with post-BD airflow obstruction. There was no significant association between biofuel burning, CD4 and ART use with airflow obstruction.

Table. Select baseline characteristics of HIV+ subjects enrolled at the Hope Center, by age

	Adolescents (10–19 years old) *n* = 55	Adults (≥20 years old) *n* = 396	*p*-value
Age, years, median (IQR)	13 (11 – 14)	41 (35 – 46)	--
HIV-related variables			
CD4 cell count, cells/μL, median (IQR)	766 (488 – 1017)	430 (288 – 633)	<0.001
Current ART use, %	95	85	0.06
Current/former cigarette smoking, %	0	13	0.002
Biofuel burning (wood, paraffin, charcoal), %	85	85	0.9
Chronic respiratory symptoms, %			
Cough	60	30	<0.001
Phlegm	51	21	<0.001
Wheeze	31	20	0.004
Resting oxygen saturation ≤92%	11	3	0.02
Post-ambulation oxygen saturation ≤92%	38	17	<0.001
Airflow obstruction (FEV1/FVC <0.7), %			
Pre-bronchodilator	18	8	0.03
Post-bronchodilator	15	6	0.02

Conclusions: Vertically-acquired HIV and cigarette smoking are independent risk factors for airflow obstruction among HIV+ individuals. Children who acquired HIV vertically and have survived to adolescence have a substantial burden of chronic respiratory signs and symptoms despite ART use and high CD4. These data suggest that acquisition of HIV infection during early ages that are critical in lung development may impact the mechanisms and manifestations of CLD in developing countries.

801 Pulmonary Complications of HIV-1 in Youth: The PHACS AMP Study

William T. Shearer[1]; Erin Leister[2]; George Siberry[3]; Denise L. Jacobson[2]; Russell B. Van Dyke[4]; Hannah H. Peavy[5]; Suzanne Siminski[6]; Meyer Kattan[7]; Laurie Butler[6]; Andrew Colin[8]

[1]Baylor College of Medicine and Texas Children's Hospital, Houston, TX, US; [2]Harvard School of Public Health, Boston, MA, US; [3]National Institutes of Health (NIH), Bethesda, MD, US; [4]Tulane University Health Sciences Center, New Orleans, LA, US; [5]National Heart, Lung, and Blood Institute, Bethesda, MD, US; [6]Frontier Science and Technology Research Foundation, Amherst, NY, US; [7]Columbia University Medical Center, New York, NY, US; [8]University of Miami Health System Batchelor Research Institute, Miami, FL, US

Background: Perinatally HIV-infected (PHIV) youth may have an increased risk of asthma compared to perinatally HIV-exposed uninfected (PHEU) youth, particularly after antiretroviral therapy. Prior studies have diagnosed asthma by history, asthma medications, and physician examination. The present multi-center study used pulmonary function tests (PFTs) to compare the prevalence of obstructive (OBS) and restrictive (RES) pulmonary patterns in PHIV and PHEU youth.

Methods: PHIV and PHEU youth enrolled in the Pediatric HIV/AIDS Cohort Study/Adolescent Master Protocol (PHACS/AMP Study) were evaluated for evidence of OBS, RES, and reversible (REV) airway patterns by PFTs without and with bronchodilators. Flow volume loops from 11 PHACS/AMP PFT laboratories were evaluated centrally by two blinded pediatric pulmonologists for acceptability. Predicted values were centrally calculated as the percent of normal values based on age-sex-race adjusted reference values in healthy children. Pulmonary disease status from pre-bronchodilator results was defined as OBS only (FEV1 < 80% or FEV1/FVC < 80% or FEF < 65%), OBS+RES (FEV1 < 80% and FEV1/FVC < 80%), RES only (FVC < 80% and FEV1/FVC ≥ 80%), or normal (not RES or OBS). Reversible airway function was defined as a ≥10% increase in FEV1 after bronchodilator. PFT results were compared by HIV status using a Chi-square test.

Results: Of the 216 PHIV and 151 PHEU youth who had a PFT test, 188 (87%) and 132 (87%) produced reproducible and acceptable PFT test results, respectively. A post-bronchodilator PFT was available on 183/188 PHIV and 126/132 PHEU. Of those with evaluable PFTs, the median age was 15.9 (range 10-21) years of age with 45% male and 68% African-American.. The prevalence of pulmonary function abnormalities was similar for PHIV and PHEU youth (P=0.37), but PHIV had a lower prevalence of reversibility than PHEU youth (9% versus 17%, P=0.052). Abnormal PFT results for PHIV vs PHEU youth were: 31 (16%) vs 24 (18%) had OBS, 13 (7%) vs 4 (3%) had OBS+RES, and 18 (10%) vs 17 (13%) had RES PFT abnormalities; 126 (67%) and 87 (66%) had normal results, respectively.

Conclusions: The rate of pulmonary function abnormalities is similar in both PHIV and PHEU youth. The lower rate of reversibility in PHIV compared to PHEU raises the possibility that respiratory symptoms in PHIV are misclassified as asthma. Further study is warranted to determine the nature and pathogenesis of the observed pulmonary function abnormalities.

802 Distinct Airway Methylation and Gene Expression Profiles in HIV-Associated COPD

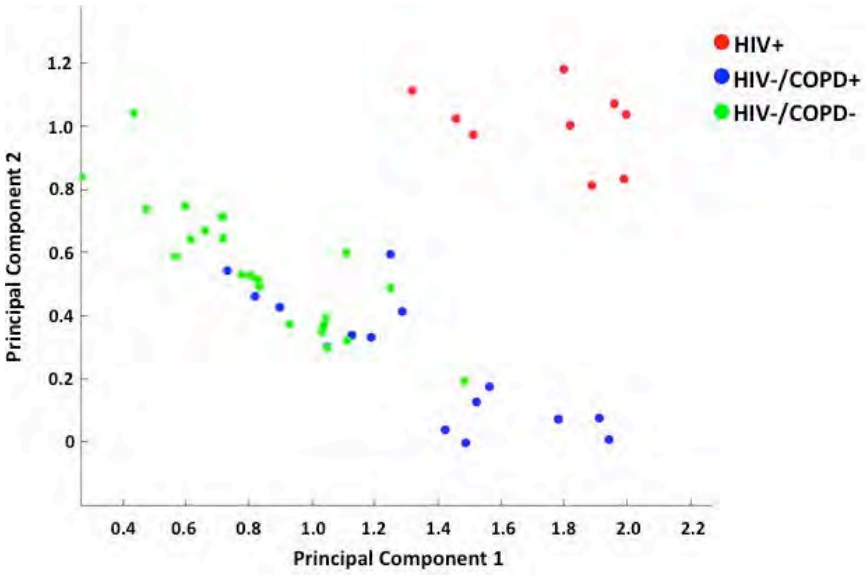
Janice M. Leung[1]; Emily Vucic[2]; Joseph C. Liu[1]; David Ngan[1]; Tawimas Shaipanich[3]; Julio Montaner[4]; Stephen Lam[2]; Don Sin[1]; Wan Lam[2]; S. F. Paul Man[1]

[1]Centre for Heart Lung Innovation, Vancouver, Canada; [2]BC Cancer Research Center, Vancouver, Canada; [3]St. Paul's Hospital, Vancouver, Canada; [4]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada

Background: Recent studies have identified an increased prevalence of chronic obstructive pulmonary disease (COPD) in HIV. Clinical manifestations of COPD in the HIV population appear to be more severe and develop earlier than in HIV-uninfected individuals. The underlying mechanism behind accelerated COPD in HIV is unknown. We hypothesize that airway epithelial DNA methylation and gene expression profiles in HIV-infected individuals can identify key molecular differences increasing the susceptibility to COPD.

Methods: Airway epithelial cells were collected from HIV-infected smokers via bronchoscopic brushings. DNA methylation profiles of these cells were obtained using the Illumina Infinium 450K Human Methylation array. Gene expression profiles were obtained using the Affymetrix GeneChip® Human Gene 2.0 ST array. Profiles were compared to HIV-uninfected smokers with and without COPD who were matched for age, sex, and smoking pack-years. DNA methylation and gene expression profiles were integrated whereby genes both hypomethylated and overexpressed or both hypermethylated and underexpressed were identified.

Results: Airway epithelial cell profiles from 10 HIV-infected smokers (average age 63 years, 7 males), all with computed tomographic evidence of emphysema, were compared to those from 15 HIV-uninfected COPD patients and 22 HIV-uninfected non-COPD controls. Principal component analysis of the top 100 methylated genes demonstrated a distinct airway epithelial profile distinguishing HIV-infected patients from both uninfected COPD patients and uninfected normal controls (Figure 1). Integration of DNA methylation and gene expression profiles demonstrated upregulation of genes involved in oxidative stress pathways in HIV-infected patients (*DNAKA4* and *DNAJC18* in the Nrf2 antioxidant stress response pathway), in contrast to HIV-uninfected COPD patients in whom proinflammatory pathways signaling through IL-17A predominated (*IL17RC* and *CSF2*).



Conclusions: DNA methylation and gene expression profiling of airway epithelial cells from HIV-infected patients reveal that increased oxidative stress may contribute to the heightened susceptibility to COPD. Targeting persistent oxidative stress may be a therapeutic option in future for mitigating age-related comorbidities such as COPD.

THURSDAY, FEBRUARY 26, 2015

Session P-Q11 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Body Composition and Risk Factors for Abnormalities

803 Altered Body Composition and Inflammation in HIV Infection With Type 2 Diabetes

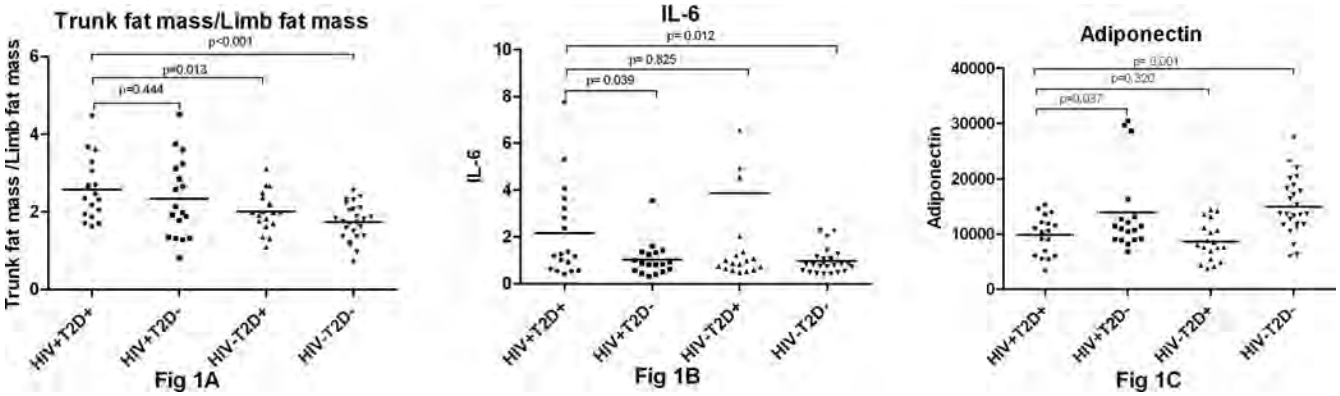
Malene Hove; Julie Abildgaard; Julie C. Gaardbo; Allan Vaag; Jan Gerstoft; Bente Klarlund Pedersen; Birgitte Lindegaard; Susanne D. Poulsen

Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark

Background: Chronic inflammation is a constant finding in HIV infection. Likewise, inflammation plays a role in the pathogenesis of type 2 diabetes (T2D). Furthermore, T2D is linked with obesity, insulin resistance, and decreased levels of anti-inflammatory adipokines. Little is known about the combined effect of HIV infection and T2D on body composition and inflammation. We hypothesized that HIV-infected persons with T2D have altered fat distribution and higher level of inflammation compared to HIV-infected persons without T2D.

Methods: Cross-sectional study including 36 HIV-infected persons on cART and with HIV RNA < 200 copies/mL (n=18 with T2D (HIV+T2D+), n=18 without T2D (HIV+T2D-)), and 44 HIV-negative persons (n=19 with T2D (HIV-T2D+) and n=25 without T2D (HIV-T2D-). Groups were matched on age and sex, and groups of HIV-infected persons on CD4 cell count (698 cells/mL vs. 656 cells/mL). DXA–scans were performed to evaluate fat distribution. Pro-inflammatory interleukin (IL)-6 and anti- inflammatory adiponectin were measured on snap-frozen plasma using Human IL-6 Kit V-PLEX and Human Adiponectin Assay. Differences between groups were analyzed using one-way ANOVA and *t* test. Data are given as mean (95%CI).

Results: Trunk fat mass/ limb fat mass ratio in HIV+T2D+ was elevated compared to HIV-T2D+ and HIV-T2D, but not when compared to HIV+T2D- (Fig. 1A). HIV+T2D+ tended to have higher trunk fat mass (17.2 kg (13.5-20.8)) compared to HIV+T2D- (12.4 kg (8.9 – 15.9), p=0.057) and HIV-T2D- (13.0 kg (11.5-14.6), p=0.020, but not compared to HIV-T2D+ (18.6 (16.2-21.0), p=0.495). IL- 6 was elevated in HIV+T2D+ compared to HIV+T2D- and HIV-T2D- but not when compared to HIV-T2D+ (Fig. 1B). Adiponectin was decreased in HIV+T2D+ compared to HIV+T2D- and HIV-T2D- but not when compared to HIV-T2D+ (Fig. 1C). Furthermore, adiponectin was negatively correlated to trunk fat mass/ limb fat mass ratio in all four groups: HIV+T2D+ p= 0.019 r= -0.546, HIV+T2D- p=0.006, r= -0.622, HIV-T2D+ p= 0.006, r= -0.603, HIV-T2D- p<0.738, r=-0.662.



Conclusions: The combination of HIV infection and T2D had adverse effects on body composition and inflammation. Impact of T2D on inflammation seemed to be more pronounced than that of HIV infection. Body composition was altered in both HIV-infected persons and those with T2D. Our results suggest that persons with both HIV infection and T2D may be especially vulnerable to altered body composition and inflammation possibly leading to increased risk of cardiovascular disease.

804 Alcohol, Substance Use, and Smoking Associations With Lipoatrophy and Lipohypertrophy

Marisela Noorhasan[1]; Daniel R. Drozd[1]; Aaron Blashill[2]; Greer Burkholder[3]; Karen Cropsey[3]; Matthew Mimiaga[2]; Katerina Christopoulos[4]; Carl Grunfeld[4]; **Heidi M. Crane**[1]
Centers for AIDS Research Network of Integrated Clinical Systems

[1]University of Washington, Seattle, WA, US; [2]Harvard Medical School, Boston, MA, US; [3]University of Alabama at Birmingham, Birmingham, AL, US; [4]University of California San Francisco, San Francisco, CA, US

Background: We sought to examine the associations between alcohol and substance use with body morphology. Unlike many previous studies, we did not combine lipoatrophy and lipohypertrophy outcomes, and were able to take into account correlated behavioral factors such as substance abuse, physical activity, and smoking.

Methods: Eligible patients were in CNICS at 6 sites and completed a touch-screen-based assessment as part of clinical care between 2006-2013 including body morphology (FRAM instrument), drug/alcohol use, physical activity level, and smoking. We used generalized estimating equations to assess differences in body morphology associated with alcohol, tobacco, and other substance use, controlling for age, race, sex, site, currently receiving ART, current and nadir CD4 cell count, viral load, hepatitis C virus, and physical activity level.

Results: The clinical assessment was completed 21,279 times by 7931 patients. Older age, detectable viral load and high current CD4 cell counts were associated with more severe lipoatrophy in adjusted analyses while black race was associated with less severe lipoatrophy (*p* values <0.001-0.008). Current cigarette smoking, marijuana use, and opiate use were all associated with more severe lipoatrophy (*p* values <0.001-0.03). Compared with patients with very low physical activity levels, all other activity levels were associated with less severe lipoatrophy (*p* values <0.001).

Older age, male sex, and higher current CD4 count were all associated with more severe lipohypertrophy in adjusted analyses (*p* values <0.001-0.04). A higher CD4 cell count nadir and current cigarette smoking were associated with less severe lipohypertrophy (*p*<0.001-0.04). Prior amphetamine use, prior and current cocaine use and prior marijuana use were all associated with more severe lipohypertrophy (*p* values <0.001-0.002). Compared with very low levels of physical activity, all other physical activity levels were associated with less severe lipohypertrophy (*p* values<0.001).

Conclusions: These results support the conclusion that lipoatrophy and lipohypertrophy are distinct. While lack of physical activity and higher CD4 counts are associated with both lipoatrophy and lipohypertrophy, associations with substance use and other clinical characteristics are different. These results may prove useful in counseling patients who wish to avoid body morphology changes and further our understanding of associations with these conditions and their possible mechanisms.

THURSDAY, FEBRUARY 26, 2015

Session P-Q12 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Complications: Liver Disease Without Viral Hepatitis

805 Antiretroviral Drugs Associated With Chronic ALT Elevations in Persons Without HCV and HBV Infection

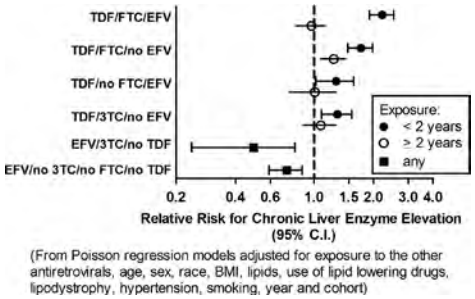
Helen Kovari[1]; Caroline Sabin[2]; Bruno Ledergerber[1]; Lene Ryom[3]; Antonella d'Arminio Monforte[4]; Matthew G. Law[5]; Stéphane De Wit[6]; Andrew N. Phillips[2]; Jens D. Lundgren[3]; Rainer Weber[1]
on behalf of the D:A:D Study Group

[1]University Hospital Zurich, Zurich, Switzerland; [2]University College London, London, United Kingdom; [3]University of Copenhagen, Copenhagen, Denmark; [4]University of Milan, Milan, Italy; [5]University of New South Wales, Sydney, Australia; [6]St Pierre University Hospital, Brussels, Belgium

Background: Whilst HIV-positive persons on ART frequently have chronic liver enzyme elevation (LEE), the underlying cause is often unclear.

Methods: D:A:D participants without HBV/HCV infection, with ≥3 alanine aminotransferase (ALT) measurements and normal baseline ALT, were followed from study entry to the earliest of chronic LEE, death, 1st Feb 2013, or last follow-up. Chronic LEE was defined as ALT >50/>35 U/L (males/females) at ≥2 visits spanning at least 6 months within 2 years. ART exposure was categorized as follows: no exposure; ongoing exposure either for < or ≥2yrs after initiation; and discontinued < or ≥2yrs earlier. Poisson regression was used to analyze LEE and its' association with ART and traditional risk factors (details see footnote in figure).

Results: 18,060 participants were followed over a total of 92,059 person-years (PY). During follow-up, 5412 participants developed chronic LEE (incidence 5.88/100 PY [95% CI 5.72-6.04]). Chronic LEE was associated with ongoing exposure to regimens containing didanosine (<2yrs RR 1.26 [1.08-1.45], >2yrs 1.27 [1.14-1.43]); stavudine (<2yrs 1.51 [1.26-1.82], >2yrs 1.17 [1.04-1.33]); tenofovir (<2yrs 1.57 [1.41-1.75], >2yrs 1.17 [1.04-1.33]); emtricitabine (<2yrs 1.17 [1.03-1.32], >2yrs 1.0 [0.86-1.18]); nevirapine (<2yrs 1.41 [1.25-1.58], >2yrs 1.01 [0.91-1.13]); and efavirenz (<2yrs 1.13 [1.02-1.25], >2yrs 0.81 [0.73-0.90]). Because the association of tenofovir with LEE was unexpected, we further analysed commonly used tenofovir-containing-regimens. The results are depicted in the figure. No evidence for an association with increased risk was found for lamivudine (<2yrs 0.88 [0.75-1.02], >2yrs 0.98 [0.87-1.11]); abacavir (<2yrs 1.08 [0.97-1.21], >2yrs 0.91 [0.83-1.01]); and all tested PIs, including lopinavir (<2yrs 0.81 [0.67-0.97], >2yrs 0.83 [0.70-0.99]), atazanavir (<2yrs 1.10 [0.94-1.28], >2yrs 0.72 [0.60-0.86]), darunavir (<2yrs 0.65 [0.51-0.84], >2yrs 0.53 [0.37-0.76]) and ritonavir (<2yrs 0.58 [0.49-0.68], >2yrs 0.79 [0.68-0.91]).



(From Poisson regression models adjusted for exposure to the other antiretrovirals, age, sex, race, BMI, lipids, use of lipid lowering drugs, lipodystrophy, hypertension, smoking, year and cohort)

Conclusions: Whilst didanosine, stavudine, nevirapine and efavirenz have been described to be hepatotoxic, we additionally observed an association between tenofovir and chronic LEE emerging within first 2 years after drug initiation. The results are consistent with other small case studies. The reasons for and clinical implications from this novel tenofovir-LEE signal should be investigated.

806 APRI and FIB4: Associated With D-Drug Exposure, Low CD4 Count and Monocyte Activation

Katherine W. Kooij[1]; Rosan van Zoest[1]; Ferdinand W. Wit[1]; Judith Schouten[2]; Neeltje Kootstra[2]; Ineke G. Stolte[3]; Maria Prins[3]; Peter Reiss[1]; Marc van der Valk[2]
AGEhIV Cohort Study Group

[1]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands; [2]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [3]Public Health Service of Amsterdam, Amsterdam, Netherlands

Background: Previous studies have suggested that HIV may be independently associated with liver fibrosis in the absence of chronic hepatitis B or C virus (HBV/HCV) coinfection.

Methods: We compared the prevalence of liver fibrosis, estimated by using APRI and FIB4 scores, in virologically suppressed HIV-infected (HIV-RNA <200c/mL in prior year) and HIV-uninfected participants of the AGE$_h$IV Cohort Study, aged ≥45 yrs, all without detectable plasma HBsAg and HCV RNA. The association between HIV and $\log_{10}$ transformed APRI [AST(U/L)/40]x[100/platelet count (PLT)(10^9cells/L)] and FIB4 [age(yrs)xAST(U/L)]/ [PLT(10^9cells/L)xALT$^{1/2}$(U/L)] scores was investigated by multivariable regression, adjusting for demographic/behavioral covariates, and exploring soluble (s)CD163, sCD14, immunodeficiency and ART exposure as possible determinants.

Results: The prevalence of liver fibrosis (APRI>1.5/FIB4>3.25) was low in both groups, though median values of both scores were significantly higher in HIV-positive individuals (Table). After adjustment for age, gender, ethnicity, heavy alcohol intake, detectable anti-HCV/anti-HBc (as markers of past infection) and BMI, we found that HIV was no longer significantly associated with logFIB4, but the association with logAPRI remained significant (+0.07, 95%CI 0.02–0.13, p=0.007). Higher sCD163 was independently associated with a higher logAPRI in the combined group (+0.03/100ng/mL, 95%CI 0.02–0.05, p<0.001), but with logFIB4 in the HIV-positive group only (+0.03/100ng/mL, 95%CI 0.01–0.05, p=0.005). sCD14 was not associated with either logAPRI or logFIB4. Within the HIV-positive group both a lower current CD4 count and longer exposure to d-drugs (ddI, ddC, d4T) were independently associated with both a higher logAPRI (CD4 count: +0.02/100cells, 95%CI 0.01– 0.04, p=0.003, d-drugs: +0.02/yr, 95%CI 0.01–0.03, p<0.001) and logFIB4 (CD4 count: +0.03/100cells, 95%CI 0.02–0.04, p<0.001, d-drugs: +0.01/yr, 95%CI 0.00–0.02, p=0.002). Prior AIDS and nadir CD4 count were not associated with logAPRI or logFIB4.

	HIV-pos, n= 433 n(%)/median (IQR)	HIV-neg, n= 473 n(%)/median(IQR)	p-val*
Age, years	53.2 (48.3 – 59.8)	52.4 (48.1 – 58.1)	0.17
Gender (male)	387 (89.4%)	404 (85.4%)	0.07
Ethnicity (black)	56 (12.9%)	37 (7.8%)	0.01
Heavy alcohol intake *(≥5/≥3 units/day (males/females))*	22 (5.1%)	31 (6.6%)	0.35
BMI, kg/m^2	24.2 (22.3 – 26.4)	24.5 (22.9 – 27.0)	0.009
Monocyte activation markers			
sCD163, ng/mL	277 (197 – 390)	244 (181 – 330)	<0.001
sCD14, ng/mL	1592 (1311 – 2023)	1327 (1066 – 1700)	<0.001
Platelet count, 10^9cells/L	211 (186 – 247)	216 (185 – 252)	0.21
APRI / logAPRI	0.32 (0.26 – 0.42) / -1.13 (-1.34 – -0.88)	0.30 (0.24 – 0.38) / -1.19 (-1.44 – -0.96)	<0.001
≤0.5	372 (85.9%)	428 (90.5%)	
0.5 – 1.5	58 (13.4%)	45 (9.5%)	
>1.5	3 (0.7%)	0 (0.0%)	0.03
FIB4 / logFIB4	1.32 (1.04 – 1.68)/ 0.28 (0.04 – 0.52)	1.23 (1.00 – 1.55)/ 0.21 (-0.00 – 0.44)	0.02
≤1.45	261 (60.3%)	326 (68.9%)	
1.45 – 3.25	166 (38.3%)	143 (30.2%)	
>3.25	6 (1.4%)	4 (0.9%)	0.02
CD4 count, cells/mm^3			
current	590 (455 – 780)		
nadir	170 (70 – 250)		
Ever exposure to d-drugs	210 (48.6%)		
Current exposure to d-drugs	3 (0.7%)		
Cumulative duration of use (of those ever exposed), years	4.4 (1.8 – 8.1)		

d-drugs, dideoxynucleoside analogues (stavudine (d4T), didanosine (ddi), zalcitabine (ddC))
**Student's t-test, rank sum test or chi-squared test where appropriate*

Conclusions: HIV infection was independently associated with a higher APRI, but not with FIB4, in virologically suppressed HIV-infected persons compared to HIV-uninfected controls, all without chronic HBV/HCV coinfection. The association between sCD163 and APRI/FIB4 may suggest a role for activated intrahepatic macrophages in liver fibrosis. Prior d-drug exposure and ongoing immunodeficiency were identified as additional contributors to liver fibrosis.

807 HIV and Liver Fibrosis Among Prison Inmates: The IeDEA West Africa Collaboration

Antoine Jaquet[1]; Gilles Wandeler[2]; Judicael Tine[3]; Claver Dagnra[4]; Alain Attia[5]; Akouda Patassi[6]; Abdoulaye Ndiaye[7]; Koumavi K. Ekouevi[8]; Moussa Seydi[3]; François Dabis[1]

[1]Inserm U897, ISPED, Université de Bordeaux, Bordeaux, France; [2]Department of Infectious Diseases, Bern University Hospital, Bern, Switzerland; [3]Service de Maladies Infectieuses et Tropicales, CRCF, CHU de Fann, Dakar, Senegal; [4]Service de Virologie, BIOLIM, Université de Lomé, Lomé, Togo; [5]Service de Hépato-Gastroentérologie, CHU de Yopougon, Abidjan, Côte d'Ivoire; [6]Service de Maladies Infectieuses et Tropicales, CHU Sylvanus Olympio, Lomé, Togo; [7]Service de Médecine Interne, CHU Aristide Le Dantec, Dakar, Senegal; [8]Département de Santé Publique, Faculté des Sciences de la Santé, Université de Lomé, Lomé, Togo

Background: Prisons are known to be a high-risk environment for addictive behaviors as well as blood-born and sexually transmitted infections leading to liver damage. Little is known about the prevalence of liver fibrosis and associated risk factors among inmates in sub-Saharan Africa.

Methods: A liver fibrosis screening was undertaken in two state prisons in West Africa. Inmates incarcerated between September-October 2013 in Lome, Togo and between April-May 2014 in Dakar, Senegal were randomly selected to participate. Those who accepted underwent a non-invasive assessment of liver fibrosis using a portable transient elastography device. Significant liver fibrosis was defined as a liver stiffness measurement ≥9.3 kPa. Serological tests for HIV, HBV and HCV infection were subsequently performed. Demographic information, addictive behaviors (alcohol, tobacco, cannabis and intravenous drugs) as well as the use of traditional medicine were assessed through a face-to-face interview. Hazardous drinking was estimated using the alcohol use disorder identification test. An unconditional logistic model was used to estimate Odds Ratio (OR) with 95% Confidence Interval (CI).

Results: A total of 703 inmates were included in Lome (n=371) and Dakar (n=332). Their median age was 30 years [interquartile range: 24-35]. The overall prevalence of significant fibrosis was 3.3% (5.1% in Lome and 1.2% in Dakar, $p<10^{-2}$). Infections with HIV, HBV and HCV were identified in 2.9%, 12.1% and 0.6% of inmates, respectively. Hazardous drinking, current tobacco and cannabis use were reported in 58 (8.2%), 315 (44.8%) and 230 (33.0%) inmates, respectively. In a multivariate analysis, factors associated with a significant liver fibrosis were HIV infection (OR=5.4; CI 1.3-22.6), HBV infection (OR=4.1; CI 1.5-11.0), HCV infection (OR=24.9; CI 2.0-305.0), the use of traditional medicine (OR=3.2; CI 1.2-8.8) and being incarcerated in Lome (OR=4.6; CI 1.4 – 15.2) (ref. Dakar).

Conclusions: Although mainly driven by viral hepatitis, HIV infection was identified as an independent determinant of liver fibrosis. In a time of increasing availability of efficient therapy for HIV and now hepatitis infections, appropriate monitoring strategies for liver disease need to be explored in vulnerable populations, including inmates. The association between traditional medicine use and liver fibrosis highlights the need to provide better documentation of etiologic factors leading to liver damages in sub-Saharan Africa.

THURSDAY, FEBRUARY 26, 2015

Session P-Q13 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Depression and Alcohol Use Disorders

808 Clinical Correlates of Alcohol Use Disorders Among HIV-Infected Adults in Zambia

Michael J. Vinikoor[1]; Masumba Masaninga[2]; Carolyn Bolton Moore[3]; Virginia Munamununungu[4]; Alice Siyunda[4]; Lloyd Mulenga[5]; Matthias Egger[6]; Benjamin H. Chi[3]; Gilles Wandeler[6]
IeDEA Southern Africa

[1]University of North Carolina, Lusaka, Zambia; [2]Lusaka District Health Management Team, Lusaka, Zambia; [3]University of North Carolina, Chapel Hill, NC, US; [4]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia; [5]University of Zambia, Lusaka, Zambia; [6]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

Background: Alcohol use among HIV-infected individuals influences antiretroviral therapy (ART) outcomes and mortality. However, data on patterns of alcohol consumption in African settings are scarce. We described the prevalence and correlates of alcohol use, including markers of liver disease, in a cohort of urban Zambian adults on HIV treatment.

Methods: At the time of ART initiation, HIV-infected adults (18+ years old) at two public sector facilities in Zambia's capital Lusaka were screened for alcohol consumption using the World Health Organization's 3-question Alcohol Use Disorders Identification Test (AUDIT-C). We categorized drinking patterns as minimal to no consumption (NC) if AUDIT-C was negative, alcohol use disorder (AUD) if AUDIT-C was positive but fewer than 3 standardized drinks (10 grams of alcohol/drink) per day were reported, and alcohol use disorder with heavy drinking (HD) if AUDIT-C was positive and patients reported 3+ drinks per day. Using Chi square tests, we compared age, sex, WHO stage, CD4+ count, hepatitis B surface antigen (HBsAg) positivity, ALT, AST, and FIB-4 between alcohol use categories. With multivariable logistic regression we investigated the association of alcohol use category with FIB-4 >3.25, a marker of liver fibrosis.

Results: Among 595 participants (median age 34 years, 54% women, and 15% with tuberculosis), 347 (58%) reported NC, 155 (26%) reported AUD, and 94 (16%) reported HD. The HD group had a larger proportion of men (P<0.01) and were more likely to have elevated ALT (P=0.01) or AST (P=0.02) compared to the two other groups (Table 1). Adjusted for age, sex, WHO stage, and HBsAg, HDs were not significantly more likely than those reporting NC to have FIB-4 >3.25 (adjusted odds ratio 0.88, 95% CI 0.34-2.27).

Table 1. Patterns of alcohol use and their demographic and clinical correlates at the time of antiretroviral therapy initiation among 596 HIV-infected Zambian adults

	No/minimal alcohol consumption (n=347)	Alcohol use disorder (n=155)	Heavy drinking (n=94)	P
Age, years				
18-29	94 (27)	46 (30)	24 (25)	0.18
30-39	150 (43)	76 (49)	50 (53)	
40+	103 (30)	33 (21)	20 (21)	
Sex				
Female	240 (69)	65 (42)	18 (19)	<0.01
Male	107 (31)	90 (58)	76 (81)	
WHO clinical stage				
1 or 2	199 (59)	90 (60)	44 (47)	0.08
3 or 4	139 (41)	59 (40)	50 (53)	
CD4 count, cells/mm³				
<200	176 (52)	90 (59)	54 (59)	0.21
200+	163 (48)	62 (41)	37 (41)	
HBsAg status				
Negative	318 (92)	134 (86)	80 (85)	0.08
Positive	29 (8)	21 (14)	14 (15)	
AST level, U/L				
<40	251 (77)	108 (74)	54 (62)	0.02
40+	75 (23)	38 (26)	33 (38)	
ALT level, U/L				
<40	302 (92)	127 (85)	71 (81)	0.01
40+	28 (8)	23 (15)	17 (19)	
FIB-4 index				
<1.45	214 (69)	103 (72)	54 (65)	0.50
1.45-3.25	72 (23)	35 (24)	22 (27)	
>3.25	22 (7)	5 (4)	7 (8)	

All values are number (%).
Abbreviations: WHO, World Health Organization; HBsAg, hepatitis B surface antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Conclusions: Hazardous alcohol use was present in nearly half of HIV-infected patients in this urban Zambian cohort. HD was more common among men and was associated with serum transaminase elevation but not with liver fibrosis. Screening for alcohol use with a brief tool such as AUDIT-C should be expanded in settings like ours and longitudinal assessment of ART and liver outcomes is needed among such populations reporting high alcohol use.

809 Depression and Treatment Outcomes Among Tanzanian Adults Initiating HAART

Christopher R. Sudfeld[1]; Sylvia Kaaya[2]; Nilupa S. Gunaratna[1]; Wafaie Fawzi[1]; Ferdinand Mugusi[2]; Mary C. Smith Fawzi[3]

[1]Harvard School of Public Health, Roxbury Crossing, MA, US; [2]Muhimbili University of Health and Allied Sciences, Dar es Salaam, United Republic of Tanzania; [3]Harvard Medical School, Boston, MA, US

Background: Depressive symptoms are common among HIV-infected individuals; however, data on the association of depression with mortality, morbidity, and CD4 T-cell reconstitution are lacking for individuals initiating HAART in sub-Saharan Africa.

Methods: Depressive symptoms and social support were assessed at ART initiation for 2,134 HIV-infected adult men and women enrolled in a trial of multivitamins in Dar es Salaam, Tanzania conducted during 2006–2010. Symptoms comparable with major depressive disorder were defined based on a modified and validated Hopkins Symptom Checklist (HSCL-25). Participants were prospectively followed at monthly clinic visits for a median of 20.6 months and CD4 T-cell measurements were obtained every 4 months. Proportional hazard models were utilized for prospective analysis of mortality, morbidity, and anthropometric outcomes while generalized estimating equations were used to analyze differences in CD4 T-cell count reconstitution.

Results: At HAART initiation 53% of Tanzanian men (343 of 647) and 59% of women (859 of 1,487) reported symptoms consistent with major depressive disorder. Significant independent risk factors for depression at HAART initiation included female sex, being single, WHO stage IV disease, smoking, low levels of social support, and lack of HIV status disclosure (all $p<0.05$). After multivariate adjustment for sociodemographics, HIV disease severity, and social support, individuals with depression had 1.82 (95% CI: 1.24-2.66; $p<0.01$) times the hazard of death as compared to individuals not reporting depressive symptoms. Depression was also associated with increased risk of >10% weight loss (HR: 1.29; 95% CI: 1.00-1.66; $p=0.049$) and oral candidiasis (HR: 1.50; 1.15-1.96; $p<0.01$) after treatment initiation. There was no significant difference in the trajectory of CD4 T-cell count reconstitution or risk of missing clinic visits by depression status ($p>0.05$).

Conclusions: Depression is present in over half of HIV-infected Tanzanian men and women at HAART initiation. Due to both the high prevalence and high risk of adverse treatment outcomes associated with depression providing effective psychosocial interventions may have a large population-level impact on reducing mortality and improving quality of life for adults initiating HAART in sub-Saharan Africa.

TUESDAY, FEBRUARY 24, 2015

Session P-R1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Immune Reconstitution Inflammatory Syndrome in Opportunistic Infections

810 Discordant Early Immune Responses Distinguish TB IRIS and Death in HIV/TB Coinfection

Shruthi Ravimohan[1]; Neo Tamuhla[2]; Andrew Steenhoff[2]; Rona Letlhogile[2]; Kebatshabile Nfanyana[2]; Tumelo Rantleru[2]; Robert Gross[1]; Drew Weissman[1]; Gregory P. Bisson[1]

[1]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, US; [2]Botswana University of Pennsylvania Partnership, Gaborone, Botswana

Background: Advanced HIV/TB patients commenced on antiretroviral therapy (ART) are at high risk for both early mortality and TB immune reconstitution inflammatory syndrome (TB IRIS). Because TB IRIS and early mortality appear to be related to rapid and minimal immune recovery, respectively, we hypothesized that these two outcomes are characterized by distinct immunologic profiles after ART initiation.

Methods: We conducted a prospective cohort study in Botswana among ART-naïve HIV-infected adults with active TB and CD4<125 cells/mm^3. Primary exposures included change from baseline to week 4 post-ART initiation in: (1) levels of 29 soluble plasma biomarkers by Luminex and (2) TB-specific immune responses measured by interferon (IFN)-γ enzyme linked immunosorbent spot (ELISPOT) assay. Patients were classified as paradoxical TB IRIS, death, or survivors without TB IRIS (controls) based on outcomes observed within 6 months of ART initiation. Rank-sum tests and logistic regression were used for analysis.

Results: Of the 159 patients with data at baseline and week 4 post-ART initiation, 116 (73%) were controls, 33 (21%) experienced TB IRIS, and 11 (7%) died. HIV RNA decreases from baseline in controls (-2.9 $\log_{10}$copies/ml [interquartile range (IQR): -3.4, -2.4]), TB IRIS (-2.9 $\log_{10}$copies/ml [IQR: -3.4, -2.4]), and deaths (-3.1 $\log_{10}$copies/ml [-3.6, -2.0]) were all similar ($p>0.05$). Both the TB IRIS and death groups were characterized by robust increases in systemic inflammatory biomarkers, with pro-inflammatory cytokines, chemokine, and growth factors being independently associated with each outcome (Table). In striking contrast, CD4 counts and TB-specific immune reconstitution from baseline to week 4 post-ART initiation were greater among the TB IRIS patients compared to controls, but markedly diminished in those who died compared to controls.

Adjusted Odds Ratio (OR) for change from baseline to week 4 post-ART initiation levels of biomarkers associated with TB IRIS and early mortality among advanced HIV/TB patients in Botswana

Biomarker	TB IRIS OR (95% CI) #	Death OR (95% CI)*
IL-6	1.7 (1.2-2.5)**	1.6 (0.9-2.9)
TNF-α	1.5 (1.0-2.2)**	1.1 (0.64-1.9)
IFN-γ	1.4 (1.0-2.0)**	1.7 (0.92-3.1)
IL-17a	1.4 (1.0-2.1)**	1.5 (0.85-2.6)
IL-8	1.4 (1.0-2.0)**	1.8 (1.0-3.3)
GCSF	1.5 (1.0-2.1)**	2.4 (1.2-4.7)**
IL-3	1.1 (0.8-1.6)	2.4 (1.2-5.0)**
IL-12p40	1.2 (0.89-1.8)	1.7 (1.0-3.0)**
IL-15	1.3 (0.92-1.9)	2.2 (1.2-4.0)**
IL-1RA	1.1 (0.76-1.6)	2.1 (1.1-4.1)**
CD4 count	1.2 (0.85-1.8)	0.35 (0.16-0.78)**
PPD response	1.2 (0.78-1.9)	0.75 (0.37-1.5)

Change from baseline to week 4 post-ART levels of biomarkers that were associated with TB IRIS or death at p<0.25 in unadjusted analyses were stratified into quartiles and assessed for association with either outcome in logistic regression models. #Adjusting for BMI or NVP use did not change ORs for listed biomarker and TB IRIS. *Model included pre-ART CD4 count, female sex, and presence of baseline OI. PPD=purified protein derivative used to measure TB-specific cellular immune responses in ELISPOT assay. **Independent association between biomarker and outcome.

Conclusions: Divergent inflammatory biomarker profile and cellular immune response characterized early mortality, while linked innate and adaptive immune responses were seen among TB IRIS following ART initiation. Interventions that decrease inflammation without inhibiting adaptive immune function hold promise in treatment of advanced HIV/TB.

811 WITHDRAWN

812 Exuberant Pathogen-Specific Th1 CD4+ T-Cell Responses in MAC-IRIS in HIV Infection

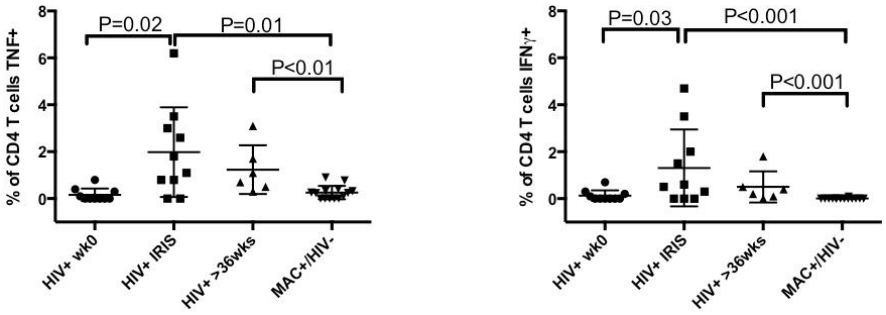
Kimberly F. Faldetta[1]; Denise C. Hsu[1]; Virginia Sheikh[1]; Gregg Roby[2]; Kenneth Olivier[1]; Irini Sereti[1]
[1]*National Institutes of Health (NIH), Rockville, MD, US;* [2]*National Institutes of Health (NIH), Bethesda, MD, US*

Background: Immune reconstitution inflammatory syndrome (IRIS) is an aberrant inflammatory immune response that can be observed after initiation of antiretroviral therapy (ART) in HIV-infected patients with severe lymphopenia and underlying opportunistic infections. The pathogenesis of IRIS is unclear but T-cells are thought to be an important contributor. Pathogen-specific T-cell responses significantly increase after ART but it is unclear how they compare to T-cell responses in HIV uninfected persons with similar infections.

Methods: In a completed observational cohort of HIV+, ART-naïve patients with CD4 count <100 cells/μL initiating ART, we identified those with *Mycobacterium avium* Complex (MAC) IRIS infections. Patients were followed for up to 96 weeks after ART initiation. Similarly, HIV- patients with MAC infections were identified from a natural history study of mycobacterial disease. Cryopreserved peripheral blood mononuclear cells were stimulated with heat-killed sonicated MAC and cytokine responses by T-cells were measured using flow cytometry. MAC-specific (sp)-CD4-T-cell % among different time points in MAC+HIV+ patients were compared using the Wilcoxon matched-pairs signed rank test and compared to MAC+HIV- patients using the Mann-Whitney test.

Results: Samples were available from 12 HIV+ patients with unmasking or paradoxical MAC-IRIS at pre-ART, IRIS, and/or a late time point (36-96 wks post-ART initiation) and from 14 HIV-MAC+ patients. HIV+ patients had a median age of 38 yrs, median baseline CD4 was 8 cells/μL, median HIV-RNA was 340,276 copies/mL and developed IRIS at a median of 41 days after ART initiation. HIV- patients had a median age of 66.5 yrs and had pulmonary MAC diagnosed according to ATS criteria.

There was no significant difference in the % CD4 T-cells producing TNF (P=0.32) or IFN-γ (P=0.07) in response to MAC between HIV- and HIV+ patients pre-ART (Fig). After ART initiation, the proportion of responding CD4 T-cells in HIV+ patients was significantly higher than HIV- patients (TNF: P<0.01; IFN-γ: P<0.001) during IRIS and remained higher even after the resolution of IRIS (TNF: P<0.01; IFN-γ: P<0.001).



CD4 T-cell responses after stimulation with heat-killed sonicated MAC.

Conclusions: CD4 T-cell responses during MAC-IRIS in HIV infected patients are significantly higher compared to HIV- people with MAC infections. These data suggest a prominent role of CD4 T-cells in MAC-IRIS immunopathology.

813 A Paradoxical Treatment of Mycobacterial Immune Reconstitution Inflammatory Syndrome

Denise C. Hsu; Kimberly F. Faldetta; **Luxin Pei**; Delmyra Turpin; Virginia Sheikh; Irini Sereti
National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

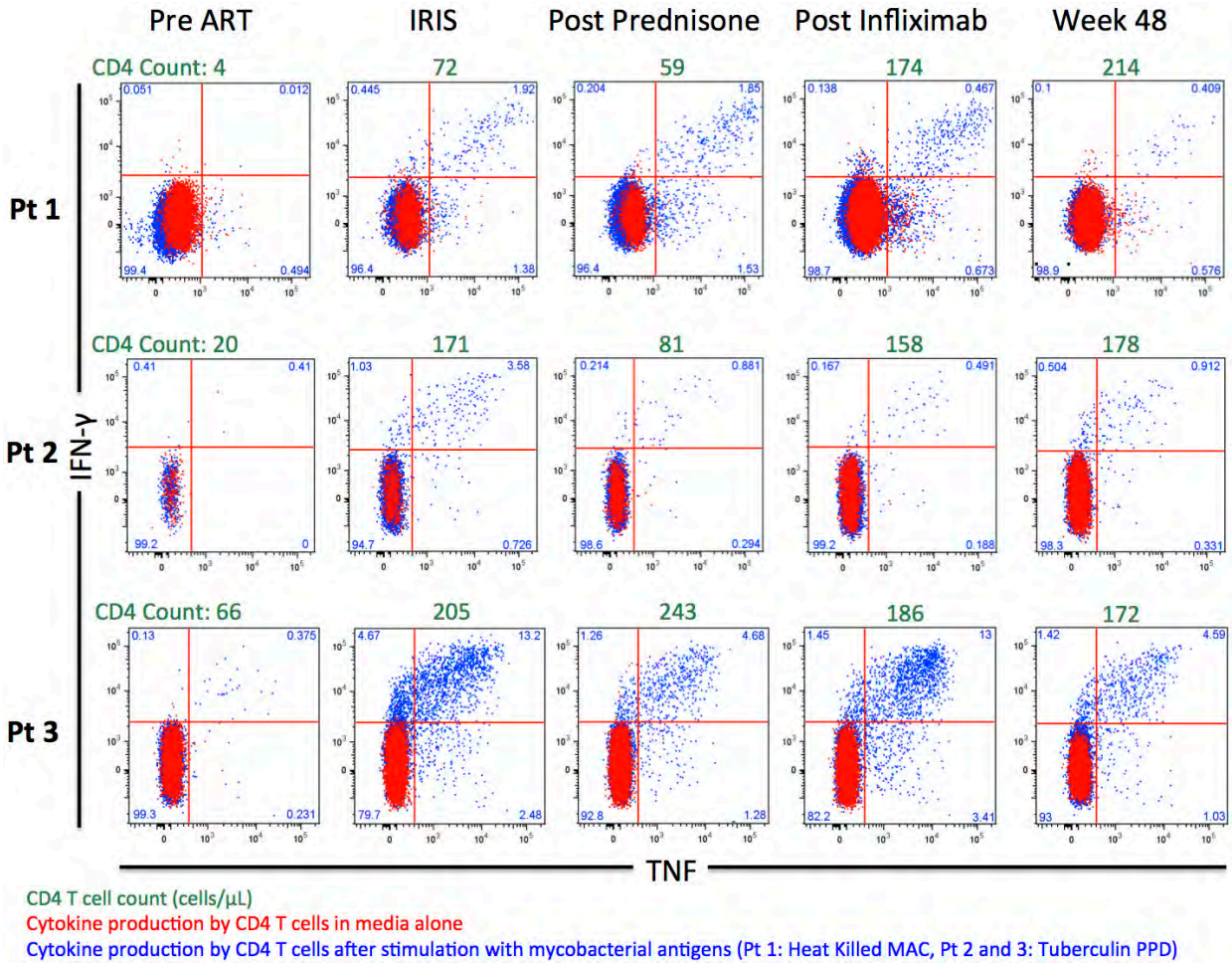
Background: Tumor necrosis factor (TNF) blockade in the treatment of autoimmune diseases has been linked to reactivation of tuberculosis (TB). Immune reconstitution inflammatory syndrome (IRIS) can complicate anti-retroviral therapy (ART) initiation in HIV patients with mycobacterial disease and can cause significant morbidity and even mortality. Corticosteroid use is the mainstay of therapy. We report the use of infliximab (anti-TNF antibody) in 3 patients with steroid-unresponsive mycobacterial-IRIS.

Methods: Patients were participants of a completed observational study evaluating predictors of IRIS in HIV-infected patients with CD4 count ≤100cells/μL starting ART. CD4 count and HIV-RNA were tested at week (wk) 0, 2, 4, 8, 12, 24, 36 and 48. T cell responses to mycobacterial antigens were assessed on batched cryopreserved samples using flow cytometry, after stimulation with tuberculin-PPD or heat-killed *Mycobacterium avium* complex (MAC).

Results: Patient (Pt) 1: 31 yo man with culture-positive MAC unmasking IRIS manifesting as cervical lymphadenopathy that failed to resolve despite anti-MAC therapy, drainage and prednisone over 4 months. Lymphadenopathy reduced after infliximab 5mg/kg every 2 wks, 3 doses. Pt 2: 41 yo man with culture positive disseminated TB (pulmonary and knee arthritis) and paradoxical TB-IRIS. He improved after high dose systemic and intra-articular corticosteroids but subsequently developed chylothorax due to obstruction of thoracic duct by enlarged lymph nodes. He improved after a single dose of infliximab 4mg/kg. Pt 3: 42 yo man with culture positive disseminated TB and paradoxical TB-IRIS manifesting as fevers and lymphadenopathy not responding to prednisone or drainage. Lymphadenopathy resolved gradually after infliximab 5mg/Kg every 2 wks, 3 doses. Prednisone was successfully tapered off in all patients after infliximab.

All patients had sterile mycobacterial cultures prior to infliximab and did not experience a clinical relapse. After infliximab administration, CD4 T cell cytokine responses to mycobacterial antigens were preserved (Fig). At week 48, HIV-RNA was <50 copies/mL and CD4 count improved for all patients (Fig).

Conclusions: Infliximab use was associated with clinical improvement in steroid-unresponsive mycobacterial IRIS without obvious adverse impact on immune recovery and virologic control in 3 patients. TNF blockade for severe mycobacterial IRIS merits further assessment in clinical trials.



CD4 T cell IFN-γ and TNF responses after stimulation with mycobacterial antigens are preserved post infliximab use.

814 CD8 T Cells in Lesions of PML-IRIS Express CCR5: Rationale for the Use of Maraviroc

Guillaume Martin-Blondel[2]; Jan Bauer[1]; Emmanuelle Uro-Coste[2]; Hervé Dumas[2]; Hans Lassmann[1]; David Brassat[2]; Pierre Delobel; Roland Liblau[3]; Bruno Marchou[2]

[1]*University of Vienna, Vienna, Austria;* [2]*Toulouse University Hospital, Toulouse, France;* [3]*Inserm, Toulouse, France*

Background: Therapeutic strategies modulating the deleterious immune response underlying immune reconstitution inflammatory syndrome (IRIS) are warranted. It has been suggested that CCR5 antagonists might be beneficial in the management of IRIS associated with progressive multifocal leukoencephalopathy (PML). Here, we analyzed the expression of CCR5 on immune cells infiltrating PML-IRIS lesions in 5 HIV-infected patients.

Methods: We performed a retrospective cross-sectional study of all HIV-infected patients diagnosed with PML-IRIS in the Toulouse University Hospital, France, between January 2000 and January 2010. Brain biopsies were collected from 5 patients and their histopathological features were compared to those of 4 HIV-infected patients with classical PML. All biopsies were performed before any steroid therapy.

Results: In all cases, histological analysis revealed demyelinating lesions and the presence of JC virus-infected cells, confirming PML. In PML-IRIS patients, the inflammatory infiltrates were dominated by $CD3^+$ T cells, which were nearly exclusively composed of $CD8^+$ T cells. Double stainings of CCR5 with CD3, CD8, CD20 (B-cells) and Iba-1 (Macrophages) showed that most of the perivascular and parenchymal infiltrating $CD8^+$ T cells strongly expressed CCR5 on their surface. Macrophages also express CCR5, but to a lesser extent. Classical PML lesions were devoid of inflammatory infiltrates.

Conclusions: Cytotoxic CD8$^+$ T cells that dominate the inflammatory response in patients with PML-IRIS highly express CCR5. By inhibiting migration and/or activation of effector cells expressing CCR5, maraviroc might be beneficial to prevent and/or treat the deleterious inflammatory reaction that occurs during immune recovery in HIV-infected PML patients. This possibility deserves further studies.

815 Monocyte Immune Responses in Cryptococcal Immune Reconstitution Inflammatory Syndrome

David B. Meya[1]; Godfrey Zziwa[2]; Samuel Okurut[2]; Stephen Cose[3]; Paul Bohjanen[4]; Sharon Wahl[5]; David R. Boulware[4]; Yuka Manabe[6]; Edward N. Janoff[7]

[1]Makerere University College of Health Sciences, Kampala, Uganda; [2]Makerere University Walter Reed Project, Kampala, Uganda; [3]Medical Research Council, Kampala, Uganda; [4]University of Minnesota, Minneapolis, MN, US; [5]National Institute for Dental and Craniofacial Research, Bethesda, MD, US; [6]Johns Hopkins University School of Medicine, Baltimore, MD, US; [7]University of Colorado, Denver, CO, US

Background: Immune Reconstitution Inflammatory Syndrome (IRIS) occurs in up to 30% of HIV-infected patients with Cryptococcal Meningitis (CM), resulting from exaggerated immune responses upon initiation of antiretroviral therapy (ART). The role of monocyte immune responses in the immunopathogenesis of cryptococcal IRIS is not well understood.

Methods: We isolated peripheral blood mononuclear cells from 11 subjects in Kampala, Uganda at CM diagnosis and at the time of CM-IRIS (CM-IRIS) and 6 subjects with CM without IRIS matched for ART duration (Controls). Upon in vitro stimulation with IFN-γ, a proxy for CD4$^+$ T cell help, frequencies of monocytes expressing IL-6 and TNF-α were quantified by intracellular flow cytometry. We defined monocytes as CD4^{lo}CD11c$^+$CD14$^+$CD16$^{+/-}$ and classical monocytes (CD14^{++}CD16$^-$); intermediate monocytes (CD14^{++}CD16$^+$) and non-classical monocytes (CD14$^+$CD16^{++}).

Results: Non-classical monocytes at CM diagnosis were less frequent in persons with future IRIS vs CM controls, median 0% (IQR, 0,0) vs 4% (IQR, 3, 5), $P<0.001$. Similarly, activated (PD-L1$^+$CD25$^+$) non-classical monocytes at CM diagnosis were less frequent in CM-IRIS vs Controls; median 0% (IQR, 0, 0) vs 11% (IQR, 6, 16), $P<0.001$. There were no differences in the frequencies of classical and intermediate monocytes between CM-IRIS vs Controls at baseline. TNF-α expression by activated classical monocytes was more frequent in CM-IRIS vs. Controls, whereas TNF-α- and IL-6-producing non-classical monocytes were higher among Controls.

During CM-IRIS, the frequencies of IL-6$^+$ classical and intermediate monocytes were increased compared with baseline pre-ART among 10 subjects with paired samples. Moreover, subjects with CM-IRIS showed a higher frequency of activated monocytes and increased frequencies of IL-6$^+$, TNF-α^+ classical monocytes and IL-6$^+$ intermediate monocytes vs. Controls. These results were seen in both unstimulated and IFN-γ stimulated monocytes, with greater magnitude in IFN-γ stimulated cells.

Conclusions: At CM diagnosis, persons who later developed CM-IRIS had increased activation and TNF-α responses compared with those who did not develop CM-IRIS. At CM-IRIS, monocyte activation was high compared to matched controls while classical and intermediate monocytes were the predominant source of cytokines. Distinct proportions and activation profiles of monocytes at CM diagnosis may lead to poor cryptococcal clearance and possible involvement of the innate immune axis in CM IRIS.

816LB Does HIV Infection Reduce the Probability of Transmission of Pulmonary Tuberculosis?

Judith R. Glynn[1]; José Afonso Guerra-Assunção[1]; Rein M. Houben[1]; Themba Mzembe[2]; Lifted Sichali[2]; Palwasha Y. Khan[1]; Ruth McNerney[1]; Julian Parkhill[3]; Taane G. Clark[1]; Amelia C. Crampin[1]

[1]London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]Karonga Prevention Study, Chilumba, Malawi; [3]Wellcome Trust Sanger Institute, Hinxton, United Kingdom

Background: HIV positive patients with pulmonary tuberculosis (TB) are thought to be less likely to transmit *M.tuberculosis*, even accounting for sputum bacillary load, because they have a shorter duration of disease. Whole genome sequencing of *M.tuberculosis* can identify who transmits to whom, and provides a new method to test this hypothesis.

Methods: In Karonga District Malawi all TB patients are identified and asked about prior contacts with patients with TB. Whole genome sequencing with ~100 fold coverage was carried out on all available cultures from 1996-2010. Transmission networks were constructed using SeqTrack, including links ≤10 mutations, and ensuring coherence of dates. The relative risk of transmitting and causing disease was estimated using ordered logistic regression, using the last 3 years of data only for assessing transmissions. In addition, the probability that a TB case acquired TB from their named contacts with smear-positive TB was calculated, by HIV status.

Results: Overall 1687 high quality sequences were available: 72 % of all culture positive cases in the district over this period. After excluding cases from the last 3 years, 431/1346 patients with pulmonary TB were identified as a source of transmission, resulting in disease in ≥1 (and up to 12) further patients. 181/588 (30.8%) HIV positive patients and 91/318 (28.6%) HIV negative patients transmitted. (8% of HIV positive patients were on antiretrovirals before TB diagnosis.) Using ordered logistic regression there was little difference in transmission from HIV positive and HIV negative patients (odds ratio 1.1, 95%CI 0.81-1.5), and this hardly changed when adjusting for age, sex, lineage, sputum smear status and year.

In the analysis of named contacts, among index case-prior contact pairs, transmission was confirmed from 27/71 (38.0%) HIV positive smear-positive prior contacts and 29/63 (46.0%) HIV negative smear-positive prior contacts (risk ratio 0.83, 0.55-1.2). This reduced slightly after adjusting for closeness of contact (adjusted risk ratio 0.78, 95%CI 0.54-1.1).

In this population about 60% of smear-positive TB patients were HIV positive. If transmission from HIV positive patients was reduced by 22%, then they would still account for 47% of transmission.

Conclusions: Contrary to what is sometimes stated, HIV positive patients appear to play an important role in onward transmission of *M.tuberculosis*. Where a high proportion of pulmonary TB patients are HIV positive they may be the main source of infection.

TUESDAY, FEBRUARY 24, 2015

Session P-R2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

T-Cell Responses to Tuberculosis Infection

817 The Relationship Between T-Regulatory Cells and Latent Tuberculosis Infection in Household Contacts Exposed to Pulmonary Tuberculosis Infection in Kampala, Uganda

Rhoda Namakula[1]; Irene A. Odanga[2]; Josephine Kasolo[2]; Ekii A. Abuku[3]

[1]Makerere University–Johns Hopkins Research Collaboration, Kampala, Uganda; [2]Makerere University College of Health Sciences, Kampala, Uganda; [3]Medical Research Council (Uganda Virus Research Institute), Entebbe, Uganda

Background: Tuberculosis remains a serious public health threat worldwide. It has been estimated that 2 billion people worldwide are latently infected with *Mycobacterium tuberculosis*. A vast pool of individuals with latent tuberculosis infection (LTBI) persists in developing countries, posing a major barrier to global TB control. Immunosuppressive regulatory T-cells (T-Regs) and CD4$^+$ T-lymphocytes in general are important in the host immune response to LTBI. T-Regs down regulate the immune system to prevent excessive

immune responses which may eventually lead to autoimmune disease and immunopathology. Activated T-Regs on the other hand, as they limit host immunity they can inhibit pathogen clearance hence facilitating pathogen multiplication and dissemination. However, their role in the regulation of Latent TB infection (LTBI) in household contacts is not yet fully defined.

Methods: This was a retrospective cross sectional study. Household contacts of adult smear positive TB patients in Kampala, Uganda were enrolled and investigated for LTBI using Tuberculin Skin Test (TST) and QuantiFERON ®-TB Gold In-Tube (QFN). LTBI was defined as a positive result of both TST and QFN. Cryo-preserved peripheral blood mononuclear cells (PBMCs) were used to determine the number and phenotypic markers of T-Regs among household contacts (HHC) with or without LTBI using multi-color flow cytometry. The difference between the two groups was compared using the Mann Whitney test for non-parametric tests.

Results: The study analyzed samples from 18 HHC with LTBI and 22 HHC without LTBI and found that the natural (naïve) T-Regs were increased in the HHC with no LTBI (median 70 cells, (Inter-quartile range (IQR) 25) as compared to HHCs with LTBI (60 cells (IQR) 18), (P=0.0278). On the other hand, the induced (memory) T-Regs were higher in HHC with LTBI (median 40 cells, (IQR) 18.2) than those without LTBI (median 30 cells, (IQR) 25), (P=0.0045). In the Phenotypic analysis, the natural T-Regs were $CD4^{+}CD127^{low/-}CD45RO^{-}$ while the induced T-Regs were $CD4^{+}$ $CD127^{low/-}CD45RO^{+}$ as expected.

Conclusions: These results suggest that there is a relationship between T-Regs and TB latency. It is anticipated that the MTB antigenic persistence in the individuals with LTBI induces a continuous generation of T-Regs resulting from the rapid turnover of induced T-Regs increasing their number in this select population. Further studies are needed to access for the function of these raised T-Regs.

818 Antiretroviral Therapy Fails to Restore Mycobacterium Tuberculosis-specific Th1 and Th17 CD4 Responses

Lyle W. Murray[1]; Dominique Goedhals[2]; Iman Satti[1]; Rodney Phillips[1]; Helen McShane[1]; John Frater[1]
Phillips/Frater
[1]University of Oxford, Oxford, United Kingdom; [2]University of the Free State, Bloemfontein, South Africa

Background: HIV-1 is the biggest risk factor for the development of tuberculosis (TB). Antiretroviral therapy (ART) substantially reduces the risk of TB in HIV+ve individuals, but incidence remains greater than for those who are HIV-ve. We hypothesized that this lack of protection results from the failure of key components of Mtb-specific Th1 and Th17 CD4 T cell responses to restore in individuals on ART.

Methods: 115 subjects were recruited in a TB-endemic setting in Bloemfontein, South Africa. The Mtb-specific T cell responses of HIV+ve (n=71) subjects were evaluated before initiation of ART, and at 6 and 12 months thereafter. HIV-ve (n=44) subjects were recruited as a comparative group. The expression on CD4 and CD8 T cells of IFNγ, TNFα, IL2 and IL17 in response to Mtb antigens (PPD, ESAT-6/CFP-10 (EC) and α-crystallin (Rv2031c)) was measured using a whole-blood flow cytometry assay.

Results: CD4 count, CD4:CD8 ratio and body mass index all increased after 6 and 12 months of ART (P<0.05 for all comparisons). There was no increase in either the proportion of CD4 responders or in the frequency of IFNγ+ CD4 cells to EC, PPD or Rv2031c at 6 or 12 months.

On ART, there was an increase in the absolute number of IFNγ, TNFα and IL2 expressing CD4 cells responding to EC, PPD and Rv2031c at 6 and 12 months (P<0.05 for all comparisons). However, there was no increase in the number of IL17+ CD4 cells responding to EC and PPD (EC, P=0.35; PPD, P=0.10), although there was to Rv2031c (P<0.0001). When comparing the contribution of IL17+ CD4 cells to the overall cytokine+ CD4 response, this declined by 6 months for PPD and Rv2031c and by 12 months for EC. This failure of restoration was dominant for the Th17 Mtb-specific CD4 responses and was not seen for the Th1 CD4 populations.

ART did increase the polyfunctionality of CD4 responses to EC, PPD and Rv2031c, possibly reflecting functional restoration of the Mtb-specific CD4 response (EC 6m, P=0.03; PPD 12m, P=0.01; Rv2013c, P=0.04). However, despite evidence for reconstitution of Mtb-specific CD4 quantity and function, the absolute magnitude of all cytokine+ CD4 responses for EC, PPD and Rv2013c in HIV+ve subjects remained significantly lower after 12 months of ART than HIV-ve subjects (P<0.0001 for all cytokines).

Conclusions: Over a 12-month period, ART only partially restored the Mtb-specific CD4 T cell response, with a diminished effect on Th17 responses. This lack of full immune reconstitution may contribute to the observed elevated TB risk despite ART.

819 Treg/Th17 and T-Cell Effector Responses in Tuberculosis Patients Coinfected with HIV

Christine Lacabaratz[1]; Aurelie Wiedemann[1]; Celine Manier[1]; Laure Bourdery[1]; Mathieu Surenaud[1]; Jean-Daniel Lelièvre[2]; Giovanna Melica[3]; Yves Lévy[2]
[1]INSERM U955, Université Paris-Est Créteil, Vaccine Research Institute, Créteil, France; [2]INSERM U955, Université Paris-Est Créteil, Vaccine Research Institute, CHU H. Mondor-A.Chenevier, Créteil, France; [3]CHU H. Mondor-A.Chenevier, Créteil, France

Background: Whether the balance between Effector and Regulatory T cell (Treg) responses against Mycobacterial Tuberculosis (MTb) may impact the outcome of clinical status of Tuberculosis (TB) infection has not been fully explored. Moreover, how these responses are perturbed and correlate with the clinical status of TB in patients coinfected with HIV is unknown.

Methods: *Ex vivo* frequency and function of Treg ($CD25^{high}CD127^{low}$FoxP3+) and Th1/Th2/Th17 cells characterized by expression of surface markers (CD45RA/CCR4/CCR6/CXCR3) among CD4 T cells, were analyzed from a cohort of TB patients, coinfected or not with HIV (n=11 TB+HIV+; n=25 TB+HIV-) and healthy donors (n=16 HD). MTb-specific responses were detected after stimulation of patients and HD PBMC with PPD and/or ESAT6-CFP10 by intracellular cytokine production (ICS) or secretion (Multiplex assays).

Results: As compared to HD, the *ex vivo* mean (±SD) frequency of Treg, Th2 and Th17 was significantly higher in TB patients (6.3±1.6%; 16.4±6.7%; 13.6±3.6%, respectively *vs.* 4.9±1.2%; 10.0±2.8%; 10.3±2.5% in HD) whereas the frequency of Th1 was lower (19.9±10.4% and 33.6±10.2%, respectively) (P<0.05 for all comparisons). Accordingly, cytokine production by PBMC stimulated with PPD was mainly oriented towards a Treg-, Th2- and Th17-related cytokine pattern (IL-10, IL-27, IL-13, IL-17A and IL-22) in TB patients as compared to HD. This profile was highly perturbed in TB+HIV+ patients who exhibited a significantly lower frequency of Treg (4.9±1.6%), Th2 (5.4±1.1%) and Th17 (7.0±3.2%) as compared to TB+HIV- patients. This was confirmed by a lower secretion of IL-5, IL-9, IL-13, IL-17 in HIV+ TB+ patients (P<0.05). Correlation between these immune responses, HIV status and the presence of sputum bacillary load (SBL+) showed: i) Mono-infected TB+HIV- patients were at a higher frequency SBL- (83%); ii) the production (mean ±SD) of IL-1β and IL-27 by ESAT6 stimulated PBMC was significantly higher in SBL- patients either coinfected or not with HIV (13138±5913 and 1235±461 pg/ml, respectively) as compared to SBL+ patients (5037±6929 and 534±399) (P<0.05).

Conclusions: TB infection, characterized by an increased frequency of peripheral Treg and a MTb response-biased towards Th2/Th17, is impacted in patients coinfected with HIV. This pattern is frequently associated with a SBL+ status. Finally, patients without SBL are characterized by a higher IL-1β and IL-27 response to TB antigens, which may represent a signature of TB infection control in the pulmonary site.

820 HIV-Tuberculosis Coinfection Leads to Increased Turnover of Late-Senescent CD8$^+$ T Cells

Shankar Esaki Muthu[1]; Chong Yee Kien[1]; Alireza Saeidi[1]; Adeeba Kamarulzaman[1]; Vijayakumar Velu[2]; Marie Larsson[3]

[1]University of Malaya, Kuala Lumpur, Malaysia; [2]Emory University, Atlanta, GA, US; [3]Linkoping University, Linkoping, Sweden

Background: CD8+ T cells reportedly have compromised functions including degranulation in HIV/TB coinfection. The role of T-cell immunosenescence and functional CD8$^+$ T-cell responses in HIV/TB co-infection has seldom been studied.

Methods: We examined and correlated surrogate markers of HIV disease progression with immune activation, immunosenescence and differentiation using T-cell pools of 19 treatment naïve HIV seropositive individuals, 9 with confirmed active TB (HIV+/TB+) and 10 without active TB (HIV+/TB-), recruited together with 6 HIV-/TB- healthy controls without active TB.

Results: Our investigations showed increased plasma viremia and reduced CD4/CD8 T-cell ratio in HIV/TB co-infected subjects, and also a closer association with changes in the expression of immune activation markers CD38 and CD57 that were consistently expressed on late-senescent CD8$^+$ T cells. Up-regulation of CD57 and CD38 were tantamount to lack of co-stimulatory and homeostasis markers, CD27 and CD28 on CD8$^+$ T cells, besides diminished expression of CD127, CD27 and CD28 on CD57$^+$ CD4$^+$ T cells. We also showed that elevation of CD57 and abrogation of CD27, CD127 and CD28 on CD8$^+$ T cells that correlated with markers of HIV disease progression, including CD38. Next, T-cell activation experiments using recombinant HIV gag p24 revealed diminished intracellular synthesis of IFN-γ, perforin and granzyme B in HIV-specific CD8$^+$ T cells of HIV-TB co-infected subjects.

Conclusions: We suggest that involvement of TB in co-infected patients may play a role that contributing to accelerated HIV disease progression, concurrently accompanied by elevated proliferative senescence, chronic immune activation, and functional insufficiency of CD8$^+$ T cells.

821 CD8 T-Cell Terminal Differentiation and Its Regulation by DHEA in HIV-TB Coinfection

Guadalupe V. Suarez[1]; Matias T. Angerami[1]; Maria B. Vecchione[1]; Omar Sued[2]; Horacio Salomon[1]; Maria F. Quiroga[1]

[1]INBIRS (UBA-CONICET), Buenos Aires, Argentina; [2]Fundacion Huesped, Buenos Aires, Argentina

Background: Tuberculosis (TB) is the first cause of death in HIV+ patients. *Mtb* infection elicits CD8 T cell (CD8Tc) responses that contribute to control latent TB (LTB). We previously showed that Dehydroepiandrosterone (DHEA) *in vitro* reduces FoxP3 expression while raises *Mtb*-induced IFN-γ release in HIV-TB patients. In this study we explored the anti-tubercular function and effector/memory phenotype of CD8Tc during HIV-TB co-infection and their modulation by DHEA.

Methods: 47 HIV+ with active TB (HIV-TB), 12 HIV+/TST+ (HIV-LTB), 12 HIV+/TST- (HIV+) and 25 healthy (HD) individuals were studied. Memory subsets, determined by CD27 and CD45RA staining, and *ex-vivo* IFN-γ production and CD107a/b staining in CD8Tc were assessed by flow cytometry. DHEA plasma levels were measured and the expression of transcription factors involved in effector/memory setting was evaluated by RT-PCR. Data was analyzed by using non-parametric tests.

Results: Bulk CD8Tc in HIV+, HIV-LTB and HIV-TB patients showed different memory subset distribution compared to HD ($p<0.05$ by partial permutation test), with lower naïve (CD27+CD45RA+, T_N) proportions in HIV-LTB and HIV-TB ($p<0.05$ by Kruskal-Wallis followed by Dunns -KWD-) and higher effector memory (CD27-CD45RA-, T_{EM}, $p<0.001$ by KWD) and terminal effector (CD27-CD45RA+, T_{TE}, $p<0.05$ by KWD) frequencies only in HIV-TB patients. Despite this increase, T_{TE} cells from HIV-TB showed lower CD45RA levels ($p<0.01$ vs. HD by KWD) suggesting a not fully differentiated phenotype. These changes were not related to TB localization or BAAR status but HAART partially restored T_N and T_{EM} levels in CD8Tc from HIV-TB ($p<0.05$ by Wilcoxon matched-pairs signed rank test -Wmp-). Also, HIV-TB patients showed increased T_{EM} and T_{TE} frequencies in CD107a/b+ and IFNγ+ *Mtb*-specific CD8Tc respectively ($p<0.05$ vs. HD by KWD). DHEA plasma levels positively correlated with the % of T_{TE} in bulk CD8Tc (Spearman $r=0.47$, $p=0.027$) and DHEA *in vitro* enhanced *Mtb*-specific CD8Tc degranulation ($p<0.05$ vs. *Mtb* by Wmp) and T_{TE} CD107a/b+ proportions ($p<0.05$ vs. media by KWD) in HIV-TB. DHEA also raised Tbet expression and Tbet/EOMES ratio ($p<0.01$ vs. media by KWD) in *Mtb*-stimulated CD8+ cells.

Conclusions: These data indicate that DHEA can induce terminal differentiation in CD8Tc during HIV-TB co-infection. To date, this is the first in-depth study of CD8Tc effector/memory phenotype in HIV-TB patients and its modulation by DHEA. We propose the use of DHEA as an adjunct therapy during *Mtb* infection in people living with HIV.

TUESDAY, FEBRUARY 24, 2015

Session P-R3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

TB Diagnostic Challenges

822 Unsuspected Prevalent TB among HIV-Infected Pregnant Women, South Africa

Jennifer D. Hoffmann[1]; **Silvia E. Cohn**[1]; Fildah Mashabela[2]; Ziyaad Waja[2]; Christopher J. Hoffmann[1]; Neil Martinson[2]; Richard E. Chaisson[1]
Tshepiso Study Team

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Perinatal HIV Research Unit (PHRU), Johannesburg, South Africa

Background: HIV and tuberculosis (TB) are leading infectious causes of death among women of reproductive age worldwide. Nearly 30% of pregnant women presenting for prenatal care in South Africa are HIV-infected. In Soweto, 0.8-2.2% of pregnant women with HIV also have active TB. South African guidelines recommend symptom screening for TB (cough, fever, night sweats, weight loss or poor weight gain) at each prenatal visit with TB investigations if any symptom is present.

Methods: Tshepiso is a prospective cohort study of HIV-infected pregnant women with active TB (cases) matched 1:2 by age, gestational age and antenatal clinic with HIV-infected pregnant women without TB (controls). Women are enrolled prenatally and followed peripartum and postpartum. Sputum culture for *Mycobacterium tuberculosis* is performed at enrollment using MGIT for all participants. We describe here cases of active TB (prevalent TB cases) in HIV-infected pregnant women selected as controls who were not considered to be TB suspects by antenatal clinic staff.

Results: From January 2011 to June 2014, we enrolled 160 HIV-infected pregnant-women as controls, matched to 72 HIV-infected pregnant women with TB (cases). During screening 7/160 controls (4%) were found to have active TB (prevalent TB cases) with positive sputum MGIT culture for MTB with median (range) days to positivity 17 (10,31). None of the prevalent TB cases reported symptoms at baseline (cough, fever, night sweats, weight loss) while 14% of the remaining control subjects reported at least one symptom. None of the prevalent TB cases reported previous history of TB, while 18% of women in the cohort (28% of cases, 14% of controls) reported being treated for TB at least one time in the past (table 1). CD4 counts in prevalent TB controls were similar to other controls and higher than women recruited as TB cases.

Table 1: Characteristics of Study Participants

	Prevalent TB case N=7	Cases N=72	Controls N=153
Age (years)			
Med [IQR]	29 (25.31)	29 (25,32)	29 (26.31)
Gestational age at enrollment (weeks)			
Med [IQR]	32 (26.32)	29 (25,34)	30 (26.34)
CD4 at baseline			
Med [IQR]	361 [303,510]	242 [139, 411]	375 [276,499]
Undetectable viral load at baseline*			
N (%)	1 (14%)	15 (21%)	61 (40%)
Viral load at baseline*			
Med [IQR]	1025 [365,14520]	2302 [210,26745]	216 [105,2675]
ART status at baseline			
PMTCT N (%)	1(14%)	18 (25%)	50 (33%)
HAART N (%)	5 (72%)	46 (64%)	89 (58%)
None N (%)	1 (14%)	8 (11%)	14 (9%)
Previous history of treatment for TB			
N (%)	0	20 (26%)	21 (14%)
Ever taken IPT/Currently taking			
N (%)	2 (29%)	5 (7%)	48 (31%)

*Of those with detectable viral load results

Conclusions: Four percent of women referred from prenatal clinics as non-TB controls were found to be sputum culture positive, demonstrating that TB symptom screen alone missed cases of TB among HIV-infected pregnant women in Soweto. In a high burden TB disease setting and a population where young women have a considerable history of TB disease, prenatal care represents an opportunity for TB diagnosis and prevention, yet additional TB screening strategies are needed for identifying TB in pregnancy and earlier initiation of treatment.

823 Evaluation of WHO 4-Symptom Tool to Rule Out TB: Data From the XPHACTOR Study

Yasmeen Hanifa[1]; Katherine Fielding[1]; Violet Chihota[2]; Nontobeko Ndlovu[2]; Alan Karstaedt[3]; Lungiswa Adonis[4]; Linda Erasmus[5]; Mark Nicol[5]; Gavin Churchyard[2]; Alison Grant[1]

[1]London School of Hygiene & Tropical Medicine, London, United Kingdom; [2]Aurum Institute for Health Research, Johannesburg, South Africa; [3]Chris Hani Baragwanath Hospital, Johannesburg, South Africa; [4]Mamelodi Hospital, Pretoria, South Africa; [5]National Health Laboratory Service, Johannesburg, South Africa

Background: The WHO 4-symptom screening tool, comprising any cough, weight loss, fever or night sweats, is a simple evidence-based tool designed for use in resource limited settings to rule out TB in people with HIV, so IPT can be safely initiated. We assessed WHO tool performance using data from the XPHACTOR study, which evaluates a novel algorithm to prioritise TB investigation amongst HIV clinic attendees in South Africa.

Methods: A systematic sample of adult clinic attendees were screened for TB using WHO tool. Sputum was tested with Xpert MTB/RIF if high priority for TB according to XPHACTOR algorithm (any of: cough, BMI<18.5, CD4<100, weight loss ≥10%). All were followed to 3 months, with reinvestigation if indicated. All had sputum and blood cultured for TB at 3 months. TB cases were classified as definite if Xpert+ or culture+ *for M. tuberculosis* at any point; probable if TB treatment commenced based on compatible radiology; possible if treated without bacteriological or radiological evidence. We calculated negative predictive value, the proportion who did not have TB out of those WHO-tool negative, to evaluate tool performance for ruling out TB.

Results: Among 3460 participants, at enrolment 898 (26%) were pre-ART and 2562 (74%) on ART; 70.5% were female. Amongst pre- vs. on ART, median age was 35 vs. 41 yrs, median CD4 399 vs. 466, 38.1% (342/898) vs. 29.9% (765/2562) were WHO tool +, and 8.1% (72/893) vs. 39.7% (1015/2558) had previous TB treatment (P<0.001).

Prevalence of TB in pre- and on-ART groups respectively was 56/898 (6.2%, 95%CI 4.7%-8.0%) and 67/2562 (2.6%, 95%CI 2%-3.3%). Amongst pre- vs. on ART TB diagnoses, 76.8% (43/56) vs. 89.6% (60/67) were definite, 16.1% (9/56) vs. 9% (6/67) probable, and 7.1% (4/56) vs. 1.5% (1/67) possible (P=0.13).

Negative predictive value of WHO tool (Table) was greater than 98% for all TB, when restricted to definite TB, and when stratified by pre vs. on ART group. Positive predictive values were low (see Table).

Table: Performance of WHO tool

	Sensitivity n/N % (95% CI)	Specificity n/N % (95% CI)	NPV n/N % (95% CI)	PPV n/N % (95% CI)
All TB [1] (123/3460)	98/123 79.7% (71.5-86.4)	2328/3337 69.8% (68.2-71.3)	**2328/2353 98.9% (98.4-99.3)**	98/1107 8.9% (7.3-10.7)
All TB [1] Pre-ART (56/898)	53/56 94.6% (85.1-98.9)	553/842 65.7% (62.4-68.9)	**553/556 99.5% (98.4-99.9)**	53/342 15.5% (11.8-19.8)
All TB [1] On ART (67/2562)	45/67 67.2% (54.6-78.2)	1775/2495 71.1% (69.3-72.9)	**1775/1797 98.8% (98.2-99.2)**	45/765 5.9% (4.3-7.8)
Definite TB [2] (103/3440)	78/103 75.7% (66.3-83.6)	2328/3337 69.8% (68.2-71.3)	**2328/2353 98.9% (98.4-99.3)**	78/1087 7.2% (5.7-8.9)
Definite TB [2] Pre-ART (43/885)	40/43 93% (80.9-98.5)	553/842 65.7 (62.4-68.9)	**553/556 99.5% (98.4-99.9)**	40/329 12.2% (8.8-16.2)
Definite TB [2] On ART (60/2555)	38/60 63.3% (49.9-75.4)	1775/2495 71.1% (69.3-72.9)	**1775/1797 98.8% (98.2-99.2)**	38/758 5.0% (3.6-6.8)

1 Definite, probable and possible TB
2 Probable and possible TB excluded from analysis

Table: Performance of WHO tool

Conclusions: In this setting the WHO 4-symptom tool performs extremely well for the purpose for which it was designed, to rule out TB, both amongst ART experienced and ART naïve individuals. However the low positive predictive value necessitates clear guidance on further evaluation of those who screen positive, in order to rationalise further investigation and avoid burdening health care systems in resource-limited settings.

824 Xpert MTB/RIF Versus AFB Smear to Determine Respiratory Isolation of US TB Suspects

Anne Luetkemeyer[1]; Cynthia Firnhaber[7]; Michelle Kendall[2]; Xingye Wu[2]; Debra Benator[3]; Gerald Mazurek[4]; Diane Havlir[1]; Beatriz Grinsztejn[5]; David Alland[6]
on behalf of the ACTG A5295/TBTC 34 Study Teams

[1]San Francisco General Hospital, University of California San Francisco, San Francisco, CA, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]Washington DC Veterans Affairs Medical Center, Washington, DC, US; [4]US Centers for Disease Control and Prevention, Atlanta, GA, US; [5]Instituto de Pesquisa Clinica Evandro Chagas, Rio de Janiero, Brazil; [6]Rutgers New Jersey Medical School, Newark, NJ, US; [7]University of Witswatersrand, Johannesburg, South Africa; [8]ACTG A5295/TBTC 34 Study Teams, N/a, MA, US

Background: U.S. guidelines recommend respiratory isolation during evaluation of suspected pulmonary tuberculosis (TB) until demonstration of serial negative acidfast bacilli(AFB) sputa. We evaluated the strategies of 1 vs. 2 rapid nucleic acid GeneXpert MTB/RIF(Xpert) tests in comparison to AFB smear for the initial diagnostic evaluation, including in persons with HIV, for whom prompt TB diagnosis is a priority.

Methods: Patients undergoing pulmonary TB evaluation had 2 sputa tested by Xpert(G4 cartridges) and compared to 2 sputum AFB smears; a subset had 3 AFB smears available. TB culture status was determined by 2 sputa samples, each cultured on both liquid and solid media. Those with *M. tuberculosis* on any of 4 cultures were classified as TB+. All had HIV testing. Exact McNemar's test was used for comparisons.

Results: 633 participants had 2 AFB smear results: median age 49 years, 69% male, 78% inpatient at time of evaluation, 38% HIV+. 91(14%) were TB+; 10(11%) of TB+ were HIV+. A subset of 361(57%) had 3 AFB smears.

The initial Xpert identified 75 of 88 (85.2%) TB+ cases, compared to 69.3% for 2 AFB smears (p=0.001) (Table). Two Xperts identified 82/90 (91.1%)TB+ cases. Initial Xpert identified 59/61(96.7%) AFB+/TB+ and two Xperts identified all 62 AFB+/TB+. For the subset with 3 AFB, 1 Xpert and 2 Xperts identified 41/50 (82.0%) and 46/52 (88.5%) of TB+ cases compared to 60.4% for 3 AFB smears, and 1 Xpert and 2 Xperts identified 30/31 (96.8%) and 32/32 (100%) of AFB+/TB+, respectively.

Specificity was 98.7% for the first Xpert and 98.4% for 2 Xperts, compared to 94.8% for 3 AFB smears (p =0.008 and 0.019, respectively). Of 18 AFB+/TB-, both 1 and 2 Xperts had 1 false positive result. Of 524 AFB-/TB-, 1 Xpert yielded 3 false positive results; 2 Xpert had 5. The negative predictive value(NPV) of 1 Xpert was 97.6%, NPV of 2 Xperts 98.5%, compared to the NPV of 2 smears of 94.8%(14% TB prevalence). The NPV of 3 AFB was 93.3%(4% TB prevalence). 1 Xpert had similar performance (p>0.05) in HIV+ vs. HIV- with sensitivity 87.5% vs. 85.0% and specificity 99.6% vs. 99.0%.

	AFB POSITIVE	1 XPERT POSITIVE	p value	2 XPERTS, AT LEAST ONE POSITIVE	p value
2 AFB SMEARS					
ALL n = 91	62/91 (68.1%)*	75/88 (85.2%)[a]	p=0.001	82/90 (90.1%)[b]	p<0.001
AFB POSITIVE n=62		59/61 (96.7%)[b]		62/62 (100%)	
AFB NEGATIVE n=29		16/27 (59.3%)[c]		20/28 (71.4%)[b]	
3 AFB SMEARS					
ALL n = 53	32/53 (60.4%)**	41/50 (82.0%)[a]	p=0.006	46/52 (88.5%)[b]	p<0.001
AFB POSITIVE n=32		30/31 (96.8%)[b]		32/32 (100%)	
AFB NEGATIVE n=21		11/19 (57.9%)[c]		14/20 (70.0%)[b]	

p value for comparison of AFB smear vs. Xpert, * AFB+ 61/88 (69.3%) for 1 Xpert comparison and 62/90 (68.9%) for 2 Xperts comparison, ** AFB+ 31/50 (62.0%) for 1 Xpert comparison and 32/52 (61.5%) for 2 Xperts comparison

[a] 3 Invalid Xperts, [b] 1 Invalid Xpert, [c] 2 Invalid Xperts

Table: Comparison of Xpert vs. AFB for the initial TB evaluation in 91 culture confirmed TB cases

Conclusions: A strategy of 2 Xperts missed no AFB+/TB+ patients, identifying all TB patients requiring respiratory isolation on the basis of AFB smear positive sputum. 1 and 2 Xperts were each significantly more sensitive and specific than 3 AFB smears for identifying culture-positive patients. These data support consideration of a 2 Xpert strategy to discontinue respiratory isolation of U.S.TB suspects, regardless of HIV status.

825 Needle Autopsies Highlight Challenges in Defining HIV+ TB Deaths Using Verbal Autopsy

Aaron Karat[1]; Mpho Tlali[2]; Salome Charalambous[2]; Kerrigan McCarthy[2]; Violet Chihota[2]; Gavin Churchyard[2]; Katherine Fielding[1]; Kathleen Kahn[3]; Tanvier Omar[4]; Alison Grant[1]

[1]London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]The Aurum Institute, Johannesburg, South Africa; [3]University of the Witwatersrand, Johannesburg, South Africa; [4]National Health Laboratory Service, Wits School of Public Health, Johannesburg, South Africa

Background: Cause of death data are crucial to guide public health policy. Verbal autopsy (VA) is widely used to collect these data, but has mostly been validated against gold standards of variable quality, generated from hospital notes. Full post-mortem is the best way to determine cause of death, though needle autopsy (NA) is more acceptable to relatives and can provide high quality information. In HIV+ individuals, differentiating between deaths due to tuberculosis (TB) and advanced HIV is difficult, but important to guide interventions to reduce early mortality. This ongoing cross-sectional study, nested within the TB Fast Track trial in South Africa, compared causes of death assigned by VA and NA in adults with advanced HIV.

Methods: Adult trial participants had a CD4 count of ≤150 cells/μL and were not taking TB treatment or antiretroviral therapy (ART). Consent for NA was obtained from participants at enrolment or from families after death (if participant not asked). NAs involved biopsies of liver, spleen, and lungs; aspiration of CSF; and broncheo-alveolar lavage. Laboratory tests included: histology; GeneXpert MTB/RIF; and MGIT, bacterial, and fungal cultures. Preliminary NA causes of death were assigned by investigators using demographic and NA data. VAs were performed within one year of death by lay-workers using the 2012 WHO tool; causes of death assigned by InterVA-4 and SmartVA software (using health care experience and narrative data). For comparison, causes of death were categorised as TB, AIDS/HIV-related (not TB), or 'other'. Cohen's kappa coefficient was used to measure inter-rater agreement.

Results: The first 20 decedents with NA and VA data were included in the analysis. 12/20 (60%) were female, with median: age at death 37.8 (interquartile range [IQR] 31-44) years; CD4 count at enrolment 31 (IQR 14-56) cells/mL; time from enrolment to death 45 (IQR 20-103) days; time from death to NA 4.5 (IQR 3-7) days; and time from death to VA 106.5 (IQR 60-178) days. Causes of death assigned by NA and VA are shown in Table 1. Agreement, expected agreement and kappa between: NA and InterVA-4 were 40.0%, 42.0%, and 0.00; and NA and SmartVA were 50.0%, 50.0% and 0.00, respectively.

Table 1: Causes of death assigned by needle autopsy and by verbal autopsy as interpreted by InterVA-4 and SmartVA

Decedent	Cause of death assigned by		
	Needle autopsy (preliminary)	InterVA-4	SmartVA*
1	Tuberculosis	AIDS/HIV-related (not TB)	AIDS
2	AIDS/HIV-related (not TB)	Tuberculosis	AIDS
3	Tuberculosis	AIDS/HIV-related (not TB)	AIDS
4	AIDS/HIV-related (not TB)	Tuberculosis	AIDS
5	AIDS/HIV-related (not TB)	AIDS/HIV-related (not TB)	AIDS
6	AIDS/HIV-related (not TB)	Other	AIDS
7	Tuberculosis	Other	AIDS
8	Tuberculosis	AIDS/HIV-related (not TB)	AIDS
9	Tuberculosis	AIDS/HIV-related (not TB)	AIDS
10	Tuberculosis	Tuberculosis	AIDS
11	AIDS/HIV-related (not TB)	Tuberculosis	AIDS
12	AIDS/HIV-related (not TB)	Other	AIDS
13	AIDS/HIV-related (not TB)	AIDS/HIV-related (not TB)	AIDS
14	Tuberculosis	AIDS/HIV-related (not TB)	AIDS
15	AIDS/HIV-related (not TB)	AIDS/HIV-related (not TB)	AIDS
16	AIDS/HIV-related (not TB)	AIDS/HIV-related (not TB)	Other
17	Other	Other	AIDS
18	Tuberculosis	AIDS/HIV-related (not TB)	Other
19	AIDS/HIV-related (not TB)	AIDS/HIV-related (not TB)	AIDS
20	AIDS/HIV-related (not TB)	AIDS/HIV-related (not TB)	AIDS

*SmartVA 'AIDS' category also includes deaths due to TB in an HIV-positive individual

Table 1: Causes of death assigned by needle autopsy and by verbal autopsy as interpreted by InterVA-4 and SmartVA

Conclusions: These preliminary data suggest that current VA tools do not perform well at distinguishing between deaths due to TB vs. other HIV-related causes among individuals with advanced HIV disease. Alternative methods should be explored so that the burden of TB mortality can be more accurately recorded.

826 Delta-Like 1 Protein, Vitamin D Binding Protein, and Fetuin Measurement in Cerebrospinal Fluid for Detection of *Mycobacterium tuberculosis* Meningitis

Nathan C. Bahr[1]; Ryan Halupnick; Grace Linder; Reuben Kiggundu[2]; Henry W. Nabeta[2]; Darlisha Williams[1]; Srinand Srevatsan[3]; Joshua Rhein[1]; David B. Meya[2]; David R. Boulware[1]

[1]University of Minnesota, Minneapolis, MN, US; [2]Makerere University College of Health Sciences, Kampala, Uganda; [3]University of Minnesota, Minneapolis, MN, US

Background: Tuberculosis meningitis (TBM) diagnosis is notoriously difficult, new biomarkers are needed. We evaluated the diagnostic utility of 3 novel biomarkers, 1) delta-like 1 protein (DLL1), a Notch ligand, which selectively drives antigen-specific CD4 T helper type-1 (Th1) responses; 2) vitamin D binding protein (VDBP); 3) fetuin. VDBP and fetuin are promising biomarkers of bovine tuberculosis.

Methods: Biomarker concentrations were measured by ELISA in cryopreserved CSF from 139 HIV-infected Ugandan patients with meningitis. TBM was diagnosed by GeneXpert MTB/Rif assay and/or mycobacterial culture. Cohort diagnoses included TBM (n=21), cryptococcal meningitis (n=71), and aseptic 'other' meningitis (n=47) among those testing negative for TB, *Cryptococcus*, and bacteria. We evaluated the diagnostic performance of DLL1 (n=136), VDBP (n=130), and fetuin (n=130) for TBM.

Results: Patient characteristics were similar at diagnosis except for sex, CD4 count, CSF WBC count, and CSF protein. DLL, VDBP, and fetuin CSF concentrations were significantly higher in patients with TBM than cryptococcal or 'other' meningitis **(Table 1)**. Using logistic regression, DLL1 alone provided 33% sensitivity, 98% specificity, 78% positive predictive value (PPV), and 88% negative predictive value (NPV). Combining DLL1 with interferon gamma (IFNg) and cryptococcal antigen testing improved sensitivity to 62% with slightly decreased specificity of 95%, PPV of 72% and NPV of 93%. For every two-fold increase in DLL1, the odds of TBM increased (adjusted Odds Ratio=2.6, 95%CI: 1.2-5.5; P=.011) in the multivariable logistic model (P<0.001 in univariate analysis). Further incorporating fetuin, VDBP, CSF white cell count, or CSF protein into a predictive model did not improve diagnostic performance. Among the 5 putative false positives as classified by the DLL1, IFNg, CRAG model, 2 had a clinical TBM diagnosis during hospitalization without

microbiologic confirmation. Among 117 persons with known outcome, in-hospital mortality was associated with increasing DLL1 levels (Odds Ratio=2.0 per two-fold increase, 95% CI: 1.2-3.6; P=.008) and decreasing fetuin (Odds Ratio=0.67 per two-fold increase, 95% CI: 0.47-0.96; P=0.030) in CSF.

Table 1: Median (IQR) CSF concentrations of delta-like 1 protein (DLL1), vitamin D binding protein (VDBP), and fetuin by diagnosis

Biomarker concentration	Tuberculosis meningitis	Cryptococcal meningitis	Other aseptic meningitis	P value	C statistic for TBM
DLL1, pg/mL	768 (522-1243)	421 (304-544)	350 (188-683)	<.001	.790
VDBP, µg/mL	4.36 (2.74-8.45)	1.55 (0.74-2.71)	1.07 (0.43-6.15)	<.001	.781
Fetuin, µg/mL	3.32 (2.15-4.60)	1.55 (0.82-2.37)	0.77 (0.43-2.81)	<.001	.818

P values calculated from mean log2 transformed biomarker values analyzed by ANOVA.

Conclusions: CSF DLL1 exhibited reasonable diagnostic performance, and may have a role as low cost adjunctive TBM diagnostic tools and may perform better in combination. Misclassification bias (of non-detection of TBM classified as 'other') hampers diagnostic studies, and future larger studies are required.

827LB Adherence to Once-Weekly Self-Administered INH and Rifapentine for Latent TB: iAdhere

Robert Belknap[1]; Andrey Borisov[2]; David Holland[3]; Pei-Jean Feng[2]; Joan-Pau Millet[4]; Neil Martinson[5]; Alicia Wright[6]; Michael Chen[2]; Joan Cayla[4]; Jose M. Mida[7]
and the Tuberculosis Trials Consortium (TBTC)

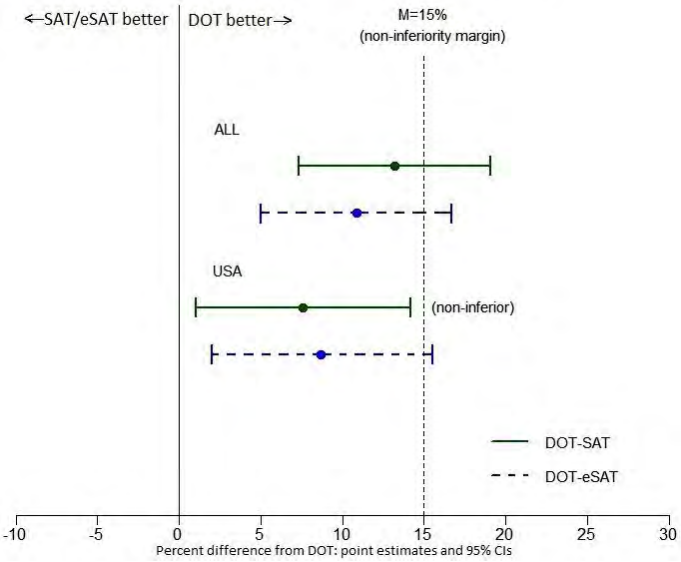
[1]Denver Health and Hospital Authority, Denver, CO, US; [2]US Centers for Disease Control and Prevention, Altanta, GA, US; [3]Emory University, Atlanta, GA, US; [4]Tuberculosis Investigation Unit of Barcelona, Barcelona, Spain; [5]University of Witwatersrand, Johannesburg, South Africa; [6]Vanderbilt University, Nashville, TN, US; [7]Hospital Clinic–IDIBAPS, University of Barcelona, Barcelona, Spain

Background: Once-weekly isoniazid and rifapentine for 3 months (3HP) by directly observed therapy (DOT) is safe and effective for treating latent tuberculosis infection (LTBI). Treatment completion with 3HP by DOT was 82.1% in the TBTC Prevent TB study. Implementation of 3HP is limited by the requirement for DOT. Models show that treatment completion by self-administered therapy (SAT) could be lower and still be cost-effective. The iAdhere study compared 3HP completion rates by DOT versus SAT or enhanced SAT with weekly text reminders (eSAT).

Methods: The study was an international clinical trial among adults with LTBI and no contraindications for 3HP or SAT. Randomization was 1:1:1, stratified by site. A non-inferiority margin of 15% was used based on cost-effectiveness modeling in the US, and enrollment targeted ≥75% from the US to have power for a pre-planned sub-analysis. The primary outcome was completion of ≥ 11 doses within 16 weeks, as determined by clinic dose records and pill counts for DOT, and by self-reports, pill counts, and medication event monitoring system (MEMS) data for SAT and eSAT.

Results: Of 1,002 patients enrolled, 4 were excluded as contacts to drug-resistant TB, 998 were eligible to complete treatment, and 772 (77%) were enrolled in the US. The study arms were demographically similar. Median age was 37 years [IQR 27, 49]. Participants included 482 (48%) women, 344 (34%) contacts to active TB, and 141 (14%) LTBI test converters; 85 (8%) had diabetes, 11 (1%) were HIV positive, 776 (78%) HIV negative, and 215 (21%) HIV unknown. Overall treatment completion was 87.2% [95%CI 83.1%-90.5%] by DOT, 74.0% [68.9%-78.6%] by SAT, and 76.4% [71.3%-80.8%] by eSAT. Treatment completion in US participants was 85.4% [80.4%-89.4%], 77.9% [77.2%-82.6%], and 76.7% [70.9%-81.7%] respectively. SAT was non-inferior to DOT in the US but not overall and eSAT did not achieve non-inferiority (figure). Discontinuation rates due to adverse effects were similar by arm, 3.6% DOT, 5.4% SAT, 4.3% eSAT (P=0.52).

Figure: Differences in Completion Rates for DOT minus SAT and DOT minus eSAT: Total and U.S. only



Conclusions: Our findings support the use of 3HP by SAT in the US. Non-inferiority was not established for SAT or eSAT overall due to higher than predicted DOT completion rates and variability in SAT and eSAT completion outside the US. Further cost-effectiveness analyses and evaluation of the role of text reminders are needed.

828LB Wirelessly Observed Therapy (WOT): A New Paradigm in TB Therapy Monitoring

Sara Browne[1]; Richard Haubrich[1]; Kathleen S. Moser[2]; Lorenzo DiCarlo[3]; Charles A. Peloquin[4]; Constance A. Benson[1]

[1]University of California San Diego, San Diego, CA, US; [2]San Diego County Health and Human Services Agency, San Diego, CA, US; [3]Proteus Digital Health Inc, Redwood City, CA, US; [4]University of Florida College of Pharmacy, Gainesville, FL, US

Background: Directly Observed Therapy (DOT) is universally recommended for TB treatment adherence, but DOT is resource intensive, expensive and unfeasible in resource-limited settings. Novel WOT technology provides date- & time-stamped recording of medication ingestions via an ingestible sensor and monitor patch worn on the patient's torso. Ingestion data is transmitted to a paired mobile device and then uploaded to a secure Internet server, where healthcare workers can confirm ingestions remotely.

Methods: We integrated the ingestible sensor (IS) with Rifamate and Rifinah, the combination dosage forms of isoniazid (INH) and rifampin (RIF), via over-encapsulation (OE) with Gelcaps. We performed dissolution testing on these. We conducted a randomized bioequivalence (BE) study in 12 patients with active TB during the continuation phase comparing ISRifamate to its native form. INH and RIF were assayed using validated HPLC methods, and the pharmacokinetic parameters were analyzed using non-compartmental methods (Phoenix/WinNonlin software). We measured the positive detection accuracy (PDA) of the WOT system using ISRifamate by comparing WOT ingestions recorded when doses were given under DOT (n=280) and evaluated WOT performance in comparison to DOT in 14 active TB patients.

Results: Patients mean age was 41 yrs, 71% male. Dissolution of OE ISRifinah 100mg/300mg was 100% at 43-45 mins for RIF and INH, meeting USP requirements. Dissolution for OE ISRifamate (100mg/300mg) reached 85-90% at 120mins. In the PK analysis of OE ISRifamate versus native form, INH and RIF were bioequivalent using the population method ratio test (95% confidence level); median INH Cmax were 3.85 and 4.27 mcg/ml; median AUC0-12h were 13.34 and 12.50 mcg/ml for native and OE, respectively. Median RIF Cmax were 12.12 and 11.79 mcg/ml; median AUC0-12h were 45.19 and 43.76 mcg/ml for native and OE ISRifamate, respectively. PDA for WOT based on 280 simultaneous DOT ingestions was 98.7% (mean), 100% (median), range (94-100%). However, the total number of WOT observations versus the total numbers of DOT doses was 148% (mean), 142% (median), range (130-187). Patients found the system easy to use with 90% giving high comfort ratings; 1 transient skin rash was observed.

Conclusions: Over–encapsulation with IS was safe and bioequivalent to standard drug. The PDA confirms WOT is highly accurate. WOT is delivered daily and confirmed more drug doses ingested than DOT overall. WOT represents a new paradigm in TB therapy monitoring.

TUESDAY, FEBRUARY 24, 2015

Session P-R4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

TB Adverse Events, Recurrence, and Mortality

829 Severe Adverse Events in Outpatient Drug-Resistant TB Treatment in South Africa

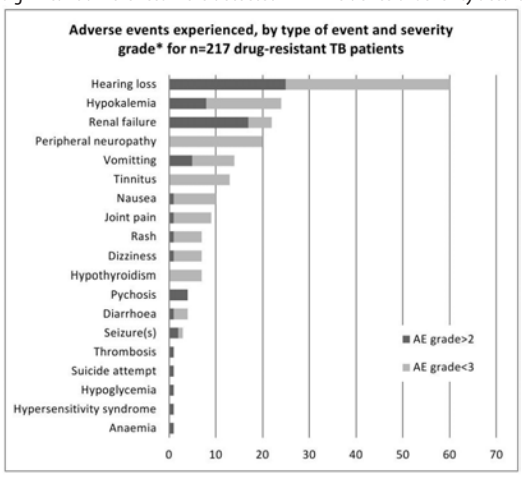
Rebecca H. Berhanu[1]; Kathryn Schnippel[2]; Andrew Black[3]; Erika Mohr[4]; Busi Mncube[1]; Ian Sanne[1]

[1]Health Economics and Epidemiology Research Organisation, Johannesburg, South Africa; [2]Right to Care, Johannesburg, South Africa; [3]Reproductive Health Institute, University of Witswatersrand, Johannesburg, South Africa; [4]Médecins Sans Frontières, Cape Town, South Africa

Background: South Africa adopted a policy of decentralization of drug-resistant TB treatment to satellite and outpatient sites in 2011. Outcomes of treatment at these new sites are not yet known. We report on the occurrence of adverse events (AE) to treatment at two outpatient, decentralized, drug-resistant tuberculosis (DR-TB) treatment sites in Johannesburg, South Africa.

Methods: Combined retrospective and prospective medical record review of the six-month intensive phase of treatment for patients (>18 years old) with DR-TB registered between May 2012 to December 2013. Patients who transferred out or were lost to follow-up during the study period were excluded. A standardized regimen of kanamycin, moxifloxacin, ethionamide and terizidone was used according to the South African national DR-TB guidelines.

Results: All 217 patients had resistance to rifampicin; 41 (20%) were also resistant to isoniazid (MDR-TB). 179 (82%) of patients were co-infected with HIV with a median CD4 count of 114 cells/μl. 240 AEs were recorded in 118 (54%) patients: hearing loss (18% of patients), hypokalemia (5%), acute kidney injury (4%) peripheral neuropathy (6%) and vomiting (4%) were the most common. Severe AEs (grade 3 to 5) accounted for 73 (30%) of AEs and were reported in 38 (18%) patients. Severe AEs were more likely to occur in those 50 years or older [Odds ratio: 5.9, 95%CI: 1.5 – 23.4], in HIV co-infected with CD4 < 100 cells/μl [2.3, CI: 1.2-4.4] and in those diagnosed with DR-TB in an inpatient setting ([1.9, CI 1.1-3.4]. Acute kidney injury was more likely to occur in men [2.3, CI 0.9-5.6] and inpatients [2.8, CI 1.1-7.2]. 22 (10%) patients died during the intensive phase of treatment. No statistically significant differences were detected in AE incidence or severity according to HIV status [0.7, CI 0.3-1.5 and 1.6, CI 0.6-0.4].



* Adverse event severity was graded according to the 2004 National Institutes of Health Division of AIDS (DAIDS) criteria as follows: grade 1 = mild, grade 2 = moderate, grade 3 = severe, and grade 4 = potentially life threatening, grade 5 = death.

Conclusions: These results suggest that severe adverse events are being experienced by a significant proportion of patients managed at outpatient DR-TB treatment sites. The most common toxicities: hearing loss, hypokalemia, and acute kidney injury, are all related to aminoglycoside treatment. As treatment of drug-resistant TB is further decentralized, training of health care workers to identify and treat adverse events is critical to improving treatment outcomes.

830 Decreased TB Recurrence After Introduction of ART in Durban, South Africa

Yuri F. van der Heijden[1]; Farina Karim[2]; Gary Parker[2]; Tilagavathy Chinappa[3]; Grace Mufamadi[3]; Linda Zako[3]; Bryan E. Shepherd[1]; Timothy Sterling[1]; Alexander Pym[2]

[1]Vanderbilt University, Nashville, TN, US; [2]KwaZulu Natal Research Institute for TB and HIV (K-RITH), Durban, South Africa; [3]Ethekwini Municipality, Durban, South Africa

Background: Recurrent tuberculosis (TB) threatens TB control. Late recurrence is usually due to reinfection. HIV-infected persons are at increased risk of reinfection, which could be due at least in part to immune compromise. We hypothesized that the introduction of antiretroviral therapy (ART) in a setting with high TB incidence and HIV co-infection would be associated with decreased TB recurrence risk.

Methods: We conducted a retrospective cohort study of all adult (≥ 18 years) TB patients seen at a single, large, urban TB clinic in Durban, South Africa (Prince Cyril Zulu Communicable Diseases Clinic) from January 2000 through December 2012. Follow-up was through December 2013. TB recurrence was defined as a TB episode occurring after treatment completion or cure of a prior TB episode. We compared time to first recurrence among those whose first visit occurred before the introduction of ART into the South African public health system (2000–2005) and after (2006–2012), with attention to early (≤365 days from first episode treatment start date) and late (>365 days) TB recurrence.

Results: There were 71,235 adult TB patients seen at the clinic during the study period, of whom 5,365 (8%) had at least one TB recurrence. There were 573 (11%) early and 4,792 (89%) late TB recurrences (median 0.9 years, IQR 0.8, 0.9 years for early; median 2.8 years, IQR 1.8, 4.4 years for late). Those whose first TB episode occurred in 2006-2012 were significantly less likely to have recurrence at the same time after cure than those whose first TB episode occurred in 2000-2005 using a Cox proportional hazards model adjusting for age at first episode, sex, and race (Hazard Ratio [HR] 0.66; 95% Confidence Interval [CI] 0.62–0.70; p<0.001). HIV status was available for 77% of patients from January 2009 through December 2012. Among 13,180 patients with known HIV status whose initial TB episode occurred during those years, 9,837 (75%) were sero-positive. In a separate Cox proportional hazards model adjusting for the same demographic factors, patients living with HIV were more likely to have a TB recurrence than those who were not HIV positive (HR 1.96; 1.52–2.54; p<0.001).

Conclusions: In this large TB cohort, most episodes of TB recurrence occurred late, suggesting exogenous reinfection rather than relapse. TB recurrence risk decreased after ART was implemented in Durban, supporting the role of improved immune status on decreasing the risk of TB reinfection.

831 Incidence of Active Tuberculosis in HIV-Infected Adults and Mortality in Thailand

Nicolas Salvadori[1]; Suwalai Chalermpantmetagul[1]; Julie Figoni[1]; Suchart Thongpaen[2]; Ampaipith Nilmanat[3]; Patinun Chirawatthanaphan[4]; Pramual Thaingamsilp[5]; Tim R. Cressey[1]; Nicole Ngo-Giang-Huong[1]; Gonzague Jourdain[1]

[1]Institut de Recherche Pour le Développement UMI 174-PHPT, Chiang Mai, Thailand; [2]Mahasarakham Hospital, Mahasarakham, Thailand; [3]Hat Yai Hospital, Hat Yai, Thailand; [4]Phaholpolpayuhasaena Hospital, Kanchanaburi, Thailand; [5]Kalasin Hospital, Kalasin, Thailand

Background: Thailand is one of the 22 high tuberculosis (TB) burden countries listed by the WHO. We estimated the incidence of active TB in HIV-infected adults, investigated the association between characteristics at antiretroviral therapy (ART) initiation and TB diagnosis, and compared survival rates of adults with and without active TB in a large HIV cohort in Thailand.

Methods: ART-naïve adults who enrolled in the PHPT cohort (NCT00433030) between 1999 and 2012 were included in this analysis. Screening for active TB was based on interview, clinical examination, chest X-ray and sputum smear. Incidence was the number of new cases divided by that of person-years of follow-up (PY). Using incidence rate ratios (IRRs) from Poisson regression models, the association between sex, age, education level, BMI, HIV RNA load, CD4 count, period of enrollment and complete blood count parameters at ART initiation and TB diagnosis was assessed. Survival rates were estimated and compared using Kaplan-Meier method and log-rank test.

Results: At ART initiation, 1702 adults (82% female) had a median age (IQR) of 31.5 years (27.1-36.8), HIV RNA load 4.8 $\log_{10}$ copies/mL (4.1-5.2) and CD4 count 144 cells/mm^3 (67-218). Median follow-up was 6.9 years (2.4-8.3). Overall incidence rate of active TB was 0.98/100 PY (95% CI 0.80-1.19) (99 cases). Incidence rates decreased with ART duration, from 5.4/100 PY within the first 6 months to 0.24/100 PY after 5 years. Median time until TB diagnosis was 7.4 months (1.4-28.4). Male gender (IRR 2.0) and BMI <18.5 kg/m^2 (IRR 4.0) at ART initiation were significantly associated with TB diagnosis (p <0.001), but not age above median (IRR 0.8, p = 0.20). Adjusting for gender and age, TB diagnosis was associated with (all p <0.001): higher (above median) HIV RNA load (IRR 2.2) and neutrophils (IRR 2.2), and lower (below median) lymphocytes (IRR 2.2), CD4 count (IRR 2.7), hemoglobin (IRR 2.8) and hematocrit (IRR 2.7). Of the 99 adults with TB diagnosis, 29 died (median survival time after diagnosis: 2.9 months (IQR 1.1-8.9)). Cumulative survival rates after ART initiation were 87% at 1 year, 73% at 5 years and 67% at 10 years in adults with active TB, versus 97%, 95% and 92% in those without active TB (p <0.001).

Conclusions: Active TB is a major cause of death in this HIV cohort in Thailand as in many settings. Most reported predictors are available in many ART programs. They should be carefully considered to accelerate TB diagnosis and treatment in patients initiating ART.

832 Antiretroviral Scale-up and Tuberculosis Mortality in High-Burden Countries

Eline Korenromp[2]; **Eran Bendavid**[1]; Isabel Yan[1]

[1]Stanford University, Stanford, CA, US; [2]Futures Institute, Glastonbury, CT, US

Background: Antiretroviral therapy (ART) is thought to reduce mortality from active TB. We investigate the extent to which the increasing availability of ART predicts reductions in national TB mortality in countries with high dual HIV-TB burden.

Methods: We analyzed annual TB mortality rates in the 41 countries that the World Health Organization (WHO) defines as high HIV-TB burden, between 1996 and 2011. We analyzed two TB mortality outcomes: (1) TB death notifications reported by national TB control programs, adjusted for TB case detection rates, and (2) WHO estimates. National Coverage with ART, the percentage of treatment-eligible HIV+ population on ART, was obtained from UNAIDS. Panel linear regressions with country fixed effects tested the relationship of TB mortality to ART coverage scale-up, controlling for time-varying HIV prevalence (5-year lagged), coverage of TB interventions, gross domestic product per capita, health spending from domestic sources, and urbanization.

Results: Across multiple model specifications and lags between ART coverage and TB mortality, we consistently observed that increasing ART coverage was followed by reduced TB mortality. Using death notifications and a 2-year lag between ART scale-up and TB mortality, we find that a 1% increase in ART coverage was associated with a 0.9% faster decline in TB deaths (p=0.002). Using WHO death estimates as outcome, a 1% increase in ART was followed by 1.1% reduced TB deaths (p<0.001). TB mortality was higher at higher HIV prevalence (p<0.001), but not related to coverage of isoniazid preventive therapy, cotrimoxazole preventive therapy, or other covariates.

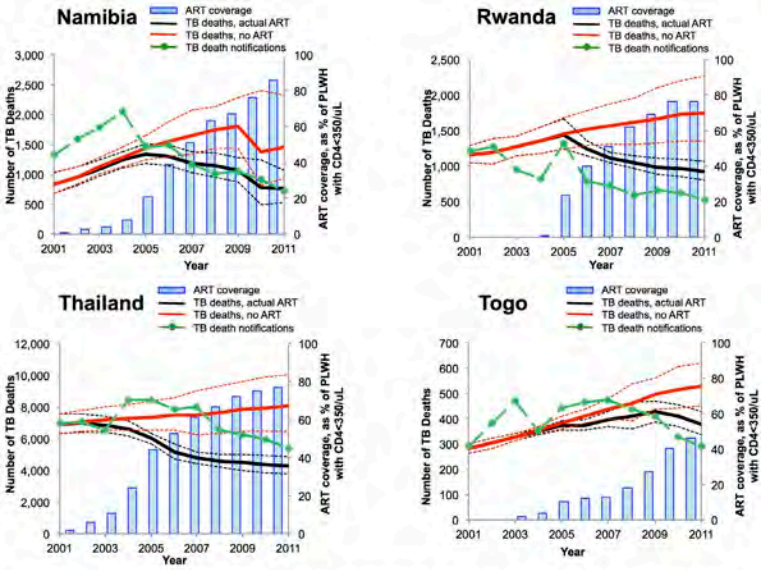


Figure: Trends in ART coverage, TB death notifications (green line), and model predictions of TB deaths with (red line) and without (black line) ART scale up in 4 (out of 41) representative countries.

Conclusions: This econometric analysis confirms the assumed beneficial impact of between ART scale up on subsequent reductions in population-level TB mortality. However, the estimated effect size was smaller than typically assumed in global impact models.

833 Culture-Negative TB Is Associated With Increased Mortality in HIV-Infected Persons

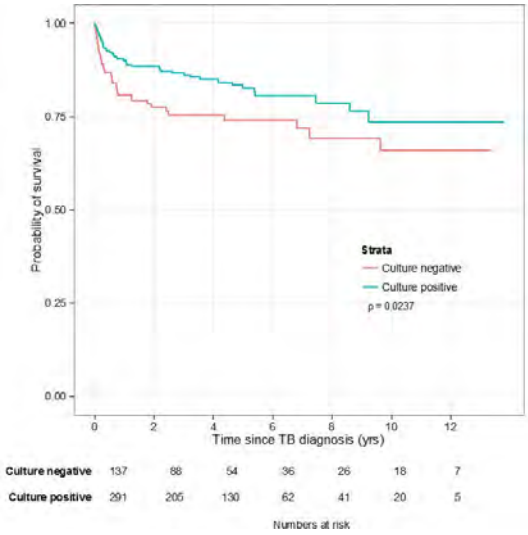
Timothy Sterling[1]; Cathy Jenkins[1]; Karu Jayathilake[1]; Eduardo Gotuzzo[2]; Valdilea Veloso[3]; Claudia P. Cortes[4]; Denis Padgett[5]; Brenda Crabtree-Ramirez[6]; Bryan E. Shepherd[1]; Catherine McGowan[1]
CCASAnet

[1]Vanderbilt University, Nashville, TN, US; [2]Universidad Peruana Cayetano Heredia, Lima, Peru; [3]Instituto Pequisa Evandro Chagas, Rio de Janeiro, Brazil; [4]University of Chile, Santiago, Chile; [5]Instituto Hondureno de Seguruidad Social, Tegucigalpa, Honduras; [6]Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico

Background: Culture-negative TB comprises 20% of TB cases in settings where TB cultures are routinely performed. In resource-limited settings, cultures are obtained less frequently, and the proportion of culture-negative TB is often much higher. Although acid fast bacillus (AFB) smear-negative TB is associated with increased mortality in HIV+ persons, there are few data on mortality risk of culture-negative TB.

Methods: We performed an observational cohort study of HIV+ adults treated for TB with standard therapy (2-month initiation phase of isoniazid, rifampin, pyrazinamide +/- ethambutol + continuation phase of isoniazid + rifampin) at or after their first HIV clinic visit. Persons were excluded if date of TB treatment relative to HAART initiation was unknown. Patients were enrolled in 2000-2013 from Brazil, Peru, Argentina, Chile, Honduras, and Mexico. Kaplan-Meier curves and Cox proportional hazards models of time from TB diagnosis to death stratified by study site were fit. For the Cox model, missing data were multiply imputed.

Results: 635 TB patients met inclusion criteria, of whom 535 had known AFB smear status (265 (50%) smear-negative) and 428 had known culture status (137 (32%) culture-negative). Median age was 36 years; 76% were male, 71% had any pulmonary TB, 56% had any extrapulmonary TB. Median CD4 count at TB diagnosis was 107 (IQR: 41-235) and 526 (83%) received concurrent HAART and TB treatment. Of the 635 patients, 139 (22%) died: 36/137 (26%) culture-negative vs. 47/291 (16%) culture-positive. The Kaplan-Meier curve of time to death by culture status is in the Figure. There was no significant difference in time to death according to AFB smear status (P=0.64). In a multivariable Cox model of all 635 patients adjusted for age, sex, site of TB disease, CD4 count, and timing of HAART initiation relative to TB treatment, persons who were culture-negative had a significantly increased risk of death (HR=1.61; 95% CI: 1.09,2.38; P=0.02). There were 12 episodes of TB recurrence occurring >180 days after initiation of TB treatment; recurrence occurred more frequently in culture-negative compared to culture-positive persons (log-rank P=0.05).



Kaplan-Meier curve of time to death by culture status among 428 persons with known culture status.

Conclusions: In this cohort, culture-negative TB was associated with a 61% increased risk of death compared to those with culture-confirmed TB. These findings raise the possibility that persons diagnosed with culture-negative TB may not have had TB, and died of other causes. This underscores the importance of accurate TB diagnosis in HIV+ persons.

THURSDAY, FEBRUARY 26, 2015

Session P-R5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Cryptococcal Meningitis: Host Response, Treatment, and Outcomes

834 Local and Systemic Humoral Responses to Cryptococcal Meningitis in Patients With AIDS

Erin E. Finn[1]; Jordan Janoff[1]; Jeremy Rahkola[1]; David B. Meya[2]; Samuel Okurut[2]; Andrew D. Kambugu[2]; Paul Bohjanen[3]; Kirsten Nielsen[3]; David R. Boulware[3]; Edward N. Janoff[1]

[1]Mucosal and Vaccine Research Colorado, Aurora, CO, US; [2]Makerere University College of Health Sciences, Kampala, Uganda; [3]University of Minnesota, Minneapolis, MN, US

Background: Antibodies may support protection against meningitis caused by *Cryptococcus neoformans* (CM), a prominent cause of disease and death in persons with AIDS, among whom antibody defects are common.

Methods: We measured total and Cryptococcus-specific IgG and IgM antibody levels by ELISA in serum and cerebrospinal fluid (CSF) from 41 antiretroviral therapy naïve adults with AIDS at the time of CM diagnosis in Kampala, Uganda. Cryptococcus-specific antibodies were directed against capsular glucuronoxylomannan (GXM) or unencapsulated organisms. Immune complexes (IC) were dissociated and neutralized with acid treatment and glycine.

Results: The median CD4+ T cell count was 16/μL and $\log_{10}$ HIV RNA was 5.33 copies/mL. CSF-analysis showed median protein of 70 mg/dL, WBC of 30/mL [43% had <5 cells], cryptococcal antigen (CrAg) titer of 1:4,000 and cryptococcal colony forming units of $\log_{10}$ 5.4/mL. Total IgG in CSF exceeded IgM by over 20 fold (median 127 vs. 5.8 μg/mL). Levels of IgG and IgM specific to GXM were greater than levels specific to unencapsulated organisms. We detected GXM-specific IgG and IgM in CSF of 46% and 24% of subjects, respectively, and in 100% of sera. The antibodies detected in CSF were specific for GXM based on cross-adsorption with heterologous polysaccharides and proteins, but the specificity of IgM exceeded that of IgG. In the CSF, GXM-IgM was produced locally, whereas the GXM-IgG was likely transferred from serum based on the ratios of GXM-specific to total IgM and IgG in CSF and serum. The majority of GXM-IgG but not IgM in the CSF was bound by local capsular GXM as levels increased by 10-fold upon dissociation of IC. IC-bound antibodies had greater avidity than antibodies freely circulating in CSF. Levels of GXM-IgG or -IgM did not correlate with CSF WBC, protein, CrAg titer or mortality (11 of 41 died [26.8%] within 30 days).

Conclusions: Specific antibodies that recognize the predominant capsular polysaccharide of *C. neoformans* (GXM) are present in the CSF of a subset of AIDS patients with CM. GXM-IgM, although present in fewer patients, was higher in concentration, specificity and avidity than GXM-IgG and was more likely produced locally at the site of infection. Enhancing levels of such antibodies may support opsonization of *C. neoformans*, promote cytokine production and cellular immune responses to the organism, and thereby faciliate protection against these common and often fatal infections.

835 Antiretroviral Therapy Alters the CSF Immune Response in Cryptococcal Meningitis

James E. Scriven[1]; Britta Urban[1]; Lisa Graham[2]; Charlotte Schutz[2]; Robert J. Wilkinson[3]; David R. Boulware[4]; David Lalloo[1]; Graeme Meintjes[2]

[1]Liverpool School of Tropical Medicine, Liverpool, United Kingdom; [2]University of Cape Town, Cape Town, South Africa; [3]Imperial College London, London, United Kingdom; [4]University of Minnesota, Minneapolis, MN, US

Background: Cryptococcal meningitis (CM) is an important opportunistic infection in sub-Saharan Africa. Animal models suggest a M2 (alternatively activated) macrophage phenotype and Th2 response are detrimental during infection but studies in humans are limited. To address this we characterized the CSF immune response in HIV-associated CM, examined the effects of ART, and explored the relationship between CSF immune response, fungal burden and mortality.

Methods: A prospective cohort study was conducted in South Africa. Persons with CM were enrolled and followed for 12 weeks. CSF immune response was examined using 11-colour flow cytometry and 17-plex luminex analysis. Fungal burden was measured using quantitative culture. Data were analysed using principal component analysis; $p<0.05$ with a false discovery rate (q) <0.1 were used to infer statistical significance.

Results: 57 subjects were enrolled: 42 not taking ART, 8 on effective ART and 7 with virological failure on ART. Median CD4 count was 34 cells/μL and median CSF WCC 18/μL. CD8 T cells were the most frequent CSF cell followed by neutrophils, macrophages and CD4 T cells (median 50%, 12%, 6.7% and 6.2% WCC respectively). Compared to individuals not on ART, the CSF of those taking effective ART had significantly increased CD4 T cells, decreased CD8 T cells, increased CD4/CD8 ratio and increased CD206 expression on CD14+ and CD14- macrophages - suggesting M2 phenotype (**table 1**). CD206 expression was inversely correlated with plasma viral load (even in persons not taking ART (r=-0.59, p=0.0001)) but was not associated with fungal burden (r=-0.02, p=0.893). Fungal burden was inversely correlated with CSF GCSF, IL6, CD4, CD8, CD4-CD8- and NK cells (r= -.49, -.41 -.61, -.55, -.49, -.40 respectively; all p <.05 and q<.1). Non-survivors had decreased CSF CD4-CD8- T cells and reduced CSF IFNγ but this was not significant when adjusted for multiple comparisons (p=.021 q=.92; p=.038, q=.97; respectively).

CSF Parameter	Effective ART		No ART		p	q
	Mean (geo)	95% CI	Mean (geo)	95% CI		
CD4 (%WCC)	13.7	7.7-24.8	4.5	3.4-6.1	0.0026	0.040
CD8 (% WCC)	19.1	11.1-32.8	47.5	40.5-55.7	0.0000	0.002
Large T cells (%WCC)	0.10	0.03-0.3	1.05	0.73-1.52	0.0000	0.023
CD4/CD8 ratio	0.72	0.29-1.75	0.08	0.05-0.13	0.0006	0.001
HLA-DR+ (% CSF CD4)	29	19-46	45	40-50	0.0075	0.060
CD206 CD14+M (MFI)	6568	3229-13227	2752	2143-3498	0.0055	0.050
CD206 CD14-M (MFI)	3327	1003-11038	938	702-1253	0.0019	0.023
CD16 CD14-M (MFI)	413	299-571	238	197-286	0.0120	0.073

Table 1. Immune parameters that differed significantly between subjects taking effective ART and those who were not. Geometric means are displayed; parametric tests were performed on log2 transformed variables. Q values refer to the false discovery rate. "Large T cells" were a secondary population of T cells with increased forward scatter. WCC=white cell count; M=macrophage

Conclusions: In CM, ART is associated with an increased CSF CD4/CD8 ratio and an increased M2 macrophage phenotype, likely mediated through effects on HIV viral load. In contrast to animal data the M2 phenotype was not associated with increased fungal load or fatal outcome. Instead, fungal burden was negatively correlated with CSF T cells (CD8, CD4 and CD4-CD8-) and concentrations of pro-inflammatory cytokines. This is supportive of the theory that a paucity of CSF inflammation is associated with severe disease in CM.

836 Detrimental Outcomes of Unmasking Cryptococcal Meningitis With Recent ART Initiation

Joshua Rhein[1]; Katherine H. Hullsiek[1]; Nathan C. Bahr[1]; Reuben Kiggundu[3]; Darlisha Williams[3]; Henry W. Nabeta[3]; Abdu Musubire[3]; David B. Meya[3]; David R. Boulware[1]

[1]University of Minnesota, Minneapolis, MN, US; [2]University of Minnesota, Minneapolis, MN, US; [3]Makerere University College of Health Sciences, Kampala, Uganda

Background: Cryptococcal meningitis (CM) remains a major cause of HIV-related mortality in Africa. Increased antiretroviral therapy (ART) availability coupled with a lack of pre-ART cryptococcal antigen screening has led to a greater proportion of patients developing CM after initiating ART. Despite this changing epidemiology, data regarding CM in patients already receiving ART are lacking. We compared the clinical presentation and outcomes in ART-naïve and ART-experienced Ugandans.

Methods: We enrolled a prospective cohort of 165 HIV-infected persons with cryptococcosis in Kampala, Uganda from Aug 2013 to Aug 2014. Subjects were classified by ART status, the timing of ART initiation, and previous CM history. The primary endpoint was 2-week mortality. Statistical comparisons were made with Kruskal-Wallis or Fisher's Exact tests.

Results: 87% (144/165) of subjects presented with their first episode of CM whereas 13% (21/165) had a previous history of CM. Of those with first CM episode, 40% (58/144) were receiving ART at presentation, having initiated ART a median of 110 (IQR, 20-519) days prior to CM diagnosis. Those receiving ART had higher CD4 (median 32 (IQR, 10-73) vs 12 (IQR, 6-39) cells/mcL; p=.02) and lower CSF fungal burdens (median 4.0 (IQR, 2.5-4.9) vs 4.8 (IQR, 3.9-5.6) $\log_{10}$ CFU/mL CSF; p<.001). 55% (32/58) had initiated ART within the last 4 months, and 22% (13/58) initiated ART within the last 14 days. Persons starting ART <4 months prior were more likely to present with altered mental status (44% vs 19% with GCS<15, p=.05) despite having lower CSF fungal burdens (median 3.7 (2.3-4.3) vs 4.5 (3.4-5.1) $\log_{10}$ CFU/mL; p=.04) compared to those initiating ART >4 months prior to CM diagnosis. CSF WBC did not differ. The 2-week mortality was significantly higher in those on ART for <14 days (54%) compared to those on ART for 15 days to 4 months (16%; p=.05), >4 months (12%; p=.01), or ART-naïve (24%). CM presenting after >4months on ART was an indication of virologic failure.

Conclusions: The occurrence of CM after initiating ART is now common in Africa. Although these patients have higher CD4 counts and lower fungal burdens, outcomes do not appear to be improved. Patients developing CM within 14 days of initiating ART are at a higher risk of death. Immune recovery in the setting of a CNS infection is detrimental, and management of this population requires future study. Implementing pre-ART cryptococcal antigen screening would decrease CM occurring early after ART initiation.

837 Impact of ART on Mortality in Cryptococcal Meningitis Patients: High-Income Settings

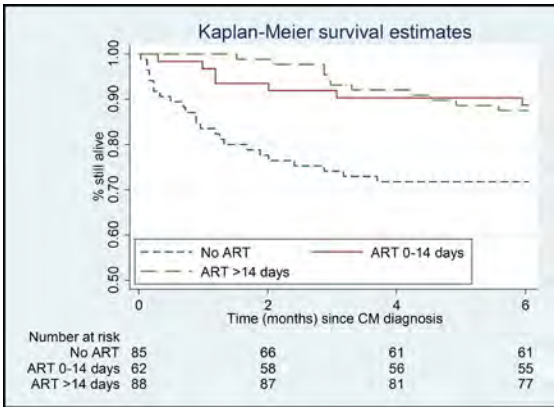
Suzanne M. Ingle[1]; Jose M. Miro[2]; Hansjakob Furrer[4]; Amy Justice[5]; Michael S. Saag[6]; Christian Manzardo[2]; Anna Esteve[7]; Lauren E. Cain[3]; Jonathan A. Sterne[1]; Margaret T. May[1]

[1]University of Bristol, Bristol, United Kingdom; [2]Hospital Clínic–L'Institut D'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain; [3]Harvard School of Public Health, Boston, MA, US; [4]Bern University Hospital and University of Bern, Bern, Switzerland; [5]Yale University School of Medicine, VA Connecticut Healthcare System, New Haven, CT, US; [6]University of Alabama at Birmingham, Birmingham, AL, US; [7]Centre d'Estudis Epidemiològics Sobre ITS/VIH/SIDA de Catalunya, Barcelona, Spain

Background: Randomised trials (RCTs) from low-income countries have shown that early ART among antiretroviral-naïve HIV-1–infected patients presenting with cryptococcal meningitis (CM) is associated with higher mortality than delayed ART. There is limited information on the impact of timing of ART on short-term mortality in patients with CM cared for in high-income settings.

Methods: Data on ART-naive patients diagnosed with CM between 1998 and 2009 were combined from cohorts contributing to the COHERE, NA-ACCORD and CNICS collaborations. Follow-up time was calculated from date of CM diagnosis to the first of death, last follow-up or 6 months post-diagnosis. We mimicked an RCT comparing regime A ("start ART within 14 days of CM diagnosis") with regime B ("defer ART until 14 -56 days after CM diagnosis"). Marginal structural models were used to compare the effects of these regimes on all-cause mortality. Models were adjusted for gender, age, mode of transmission, CD4, viral load (VL), AIDS (other than CM), year of diagnosis and whether data were European/North American.

Results: Of 235 patients (84% male) from 28 cohorts across Europe and N. America with full covariate data, 42 (18.0%) died within 6 months. Median age at CM diagnosis was 38 years (IQR 34-44). Of 150 patients (64%) who started ART, 18 (12%) died within 6 months. 7/62 (11%) patients died among those who started ART within 2 weeks of CM diagnosis, compared with 11/88 (12%) among those who started ART after 2 weeks. The graph shows crude survival over time, according to when the patient started ART. In data mimicking an RCT, there were 15 deaths (33.3 years follow-up) in regime A and 26 deaths (47.8 years) in regime B. The crude and adjusted hazard ratios comparing deferred with early treatment were 1.29 (95% CI 0.68-2.43) and 1.30 (0.66-2.55).



Kaplan-Meier survival estimates according to time of starting ART

Conclusions: We found little evidence that early ART was associated with higher mortality after CM than deferred ART, although confidence intervals were wide. Although we adjusted for potential confounding factors, confounding and selection bias may not be fully adjusted for; we aim to address this limitation by ascertaining additional information on treatment of CM after diagnosis. Mortality among patients cared for in high income settings was clearly lower than reported in the RCTs conducted in low-income countries.

838 Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis

Joshua Rhein[1]; Katherine H. Hullsiek[1]; Bozena Morawski[1]; Kyle Smith[1]; Ali Al-Hadab[1]; Abdu Musubire[2]; Darlisha Williams[2]; Kristen Nielsen[1]; David B. Meya[2]; David R. Boulware[1]

[1]University of Minnesota, Minneapolis, MN, US; [2]Makerere University College of Health Sciences, Kampala, Uganda

Background: Mortality from HIV-associated cryptococcal meningitis (CM) remains unacceptably high. Identifying new effective antifungals is of paramount importance. We evaluated the efficacy of adjunctive sertraline, previously demonstrated to be active against *Cryptococcus neoformans* both *in vitro* and in murine models.

Methods: 144 HIV-infected persons with first episode of CM were prospectively enrolled in a phase IIb, open-label clinical trial in Kampala, Uganda between Aug 2013-2014. Sertraline at doses of 100-400 mg/day was added to standard therapy (amphotericin + fluconazole 800mg/day). Early fungicidal activity (EFA) was measured as the rate of cryptococcal clearance in serial quantitative CSF cultures and calculated by mixed effect model for all participants with at least 2 CSF cultures (N=122). Sertraline concentrations in plasma were measured using high performance chromatography–mass spectrometry in 77 subjects to evaluate how rapidly sertraline achieves steady state. *In vitro* susceptibility was assessed on a subset of *C. neoformans* isolates (N=95) to determine target 90% minimum inhibitory concentration (MIC90).

Results: Those receiving any dose of sertraline had 28% faster rate of clearance compared with recent historical controls (Table): EFA -0.39 vs. -0.30 for those with vs. without sertraline (p=0.03). Sertraline reached steady state in plasma by day 7, with a median level of 215 (IQR, 126-305) ng/mL at 200mg/day and 400 (IQR, 281-556) ng/mL at 400mg/day. Plasma levels were 68% of steady state levels by day 3. The projected steady state brain tissue concentration at 200mg/day was a median of 3.5 (IQR, 2.1-5.0) mcg/mL and at 400mg/day was 6.6 (4.6-9.2) mcg/mL. Among *Cryptococcus* isolates, the MIC90 was ≤1 mcg/mL for 9.5%, ≤2 mcg/mL for 30.5%, ≤4 mcg/mL for 84%, and ≤8 mcg/mL for 99% of isolates. *In vitro* synergy studies (n=9) found a median 2-fold reduction in the MIC90 with a combination of sertraline and fluconazole. For sertraline at doses 200-400mg/day, the incidence of paradoxical IRIS or relapse through 12 weeks was 1%.

Table: Early Fungicidal Activity of the Rate of CSF Clearance in Cryptococcal Meningitis

Anti-Fungal Induction Regimen	N	EFA[1] (95% CI) $\log_{10}$ CFU/mL
Standard therapy [2] + 100 mg/day sertraline	13	-0.37 (-0.41, -0.24)
Standard therapy [2] + 200 mg/day sertraline	40	-0.40 (-0.48, -0.31)
Standard therapy [2] + 300 mg/day sertraline	38	-0.39 (-0.47, -0.32)
Standard therapy [2] + 400 mg/day sertraline	31	-0.37 (-0.47, -0.29)
Standard therapy + all sertraline regimens	122	-0.39 (-0.43, -0.34)
Standard therapy without sertraline [2,3]	189	-0.30 (-0.32, -0.28)

[1] EFA (Early Fungicidal Activity) estimated with longitudinal mixed models. Values are population means with 95% confidence intervals (95% CI).

[2] Standard therapy: Amphotericin B deoxycholate (0.7-1.0mg/kg/day)+ fluconazole 800mg/day.

[3] Historical controls, enrolled from November 2010 through July 2013.

Conclusions: Sertraline provides fungicidal activity against *C. neoformans* with improvements in CSF clearance rates and appears to reach therapeutic levels *in vivo*. This widely available off-patent oral medication ($0.05 per 100mg tablet) provides a promising adjunct for CM treatment when added to standard antifungal therapy. This pilot justifies a larger randomized trial to elucidate whether sertraline has a survival benefit for the treatment of CM.

TUESDAY, FEBRUARY 24, 2015

Session P-R6 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Syphilis and HIV Coinfection

839 Infection With HIV Among Individuals With Primary and Secondary Syphilis: USA, 2013

John R. Su; Akbar A. Zaidi; Elizabeth A. Torrone; Hillard S. Weinstock

US Centers for Disease Control and Prevention, Atlanta, GA, US

Background: Reports of primary and secondary (P&S) syphilis from large cities describe high proportions of co-infection with HIV among men who have sex with men (MSM). This analysis was performed to describe prevalence of co-infection across the U.S. during 2013.

Methods: We reviewed data reported to CDC from counties reporting both sex of sex partner and HIV status (either HIV-positive or HIV-negative per self report, at time of syphilis diagnosis) for at least 70% of cases of P&S syphilis for 2013. The proportion of P&S syphilis cases co-infected with HIV (i.e., reported cases of P&S syphilis who were also HIV-positive) was calculated and stratified by sex and sexual behavior, race/ethnicity, age group, and census region of the U.S.

Results: During 2013, 651 (58%) of 1,114 counties reporting cases of P&S syphilis from 44 states and Washington, DC met inclusion criteria. Of the 11,453 cases of P&S syphilis reported in these counties, 9,461 (83%) had both sex of sex partner and HIV status reported, of whom 42% were co-infected with HIV. Regardless of region, more than 40% of cases were co-infected (range: 41%–51%). Among individuals with P&S syphilis, 7,150 (76%) were MSM, 15% were men having sex with women only (MSW), and 9% were women. The highest prevalence of co-infection occurred among MSM (52% among MSM, compared to 11% among MSW and 5% among women). Prevalence of co-infection increased with age among MSM: 35% aged 15–24 years, 48% aged 25–29 years, 57% aged 30–39 years, and 65% aged 40 years and older were co-infected. Of MSM aged 15–24 years, 50% of blacks, 21% of Hispanics, 22% of whites, and 25% of other races were co-infected. Considering only MSM aged 15–19 years, 33% of blacks were co-infected (compared to 16% of Hispanics, 11% of whites, and 15% of other races).

Conclusions: The most current national surveillance data available indicate that, among individuals reported with P&S syphilis, co-infection with HIV is common across the U.S., even among young (e.g., 15–19 years) MSM. These findings reinforce the recommendation that anyone diagnosed with syphilis be tested for HIV. A diagnosis of P&S syphilis provides an opportunity to ensure that individuals infected with HIV are linked to care, and that the sexual contacts of co-infected individuals are tested for both syphilis and HIV, linked to care, and treated, if appropriate. Efforts to prevent HIV and syphilis must target younger populations before they become infected.

840 Risk Factors for Asymptomatic and Symptomatic Neurosyphilis Differ in HIV-Infected Patients With Syphilis

Christina Marra; Trudy Jones; Shelia Dunaway; Emily Ho; Abigail Crooks; Lauren Tantalo; Sharon Sahi

University of Washington, Seattle, WA, US

Background: Syphilis is common in HIV. Neurosyphilis (NS) is a serious complication of syphilis that can be asymptomatic (asx) or symptomatic (sx). Previous studies have examined risk factors for NS in HIV, but not separately for asx vs. sx NS.

Methods: 531 HIV-infected patients with syphilis underwent standardized history and neurological examination, lumbar puncture (LP) and blood draw. 392 (74%) had no NS (no NS symptoms and signs, CSF white blood cells (WBC) ≤20/ul, CSF-Venereal Disease Research Laboratory (VDRL) nonreactive), 54 (10%) had asx NS (no NS symptoms and signs, CSF WBC >20/ul or CSF-VDRL reactive), and 85 (16%) had sx NS (NS symptoms and signs). The impact of demographic and clinical measures on asx and sx NS risk was expressed as odds ratios (OR, 95% confidence intervals [95% CI]) using logistic regression.

Results: Patients were mainly white (81%) men (99%); 78% had early syphilis, 44% underwent LP a median of 8 (IQR 5-16) days after treatment for current syphilis and 26% had a prior episode of syphilis. Median CSF WBCs were 4 (2-7) for no NS, 29 (17-51) for asx NS and 24 (7-50) for sx NS; CSF-VDRL was reactive in 59% of asx NS and 47% of sx NS; 29% of sx NS did not have CSF abnormalities. Sx NS included vision loss (n=52), hearing loss (n=37), symptomatic meningitis (n=43) and stroke (n=1, also with symptomatic meningitis). Age and CD4 ≤350 cells/ul did not affect the ORs for asx or sx NS, while higher serum rapid plasma regain (RPR) titer and no current use of antiretrovirals (ARVs) increased the odds of both. Late syphilis increased the odds of asx but not sx NS, and both treatment for the current episode of syphilis, and a previous episode of syphilis decreased the odds of sx NS but not asx NS (Table). In multivariate analysis, the odds of asx and sx NS remained higher in those with higher RPR titers and no ARV use. Late syphilis was an independent risk for asx but not sx NS, and previous syphilis treatment conferred decreased risk for sx, but not asx NS (Table).

Table

	Asx NS		Sx NS	
	Univariate	Multivariate	Univariate	Multivariate
	OR (95% CI)		OR (95% CI)	
Serum RPR[1]	1.3 (1.1-1.4)***	1.4 (1.2-1.6)***	1.4 (1.2-1.6)***	1.4 (1.3-1.6)***
No ARV use	2.4 (1.4-4.4)**	2.8 (1.5-5.2)**	3.2 (1.9-5.1)***	3.3 (2.0-5.5)***
Late stage[2]	2.3 (1.2-4.1)**	3.4 (1.7-6.5)***	NS	--
Previous treatment[3]	NS	--	0.5 (0.3-0.8)**	0.5 (0.3-0.8)**
Previous syphilis[4]	NS	--	0.5 (0.3-1.0)*	NS

1, per 2-fold increase in titer; 2, early stage includes primary, secondary and early latent syphilis, late stage includes late latent syphilis and syphilis of unknown duration; 3, treatment for current episode of syphilis before LP; 4, an episode of syphilis before the current episode.

NS, P>0.05; *P<0.05, **P<0.01; *** P<0.001

Conclusions: HIV-infected individuals with syphilis with higher serum RPR titers and who are not currently taking ARVs have an increased risk of asx and sx NS. In contrast, syphilis stage, previous syphilis treatment, and a previous episode of syphilis differentially affect the risk of asx and sx NS. Our findings can assist clinicians in choosing which HIV-infected syphilis patients would benefit the most from CSF examination.

841 High Incidence of Syphilis Among Thai MSM Who Started ART Therapy During Acute HIV Infection

Donn J. Colby[1]; Suteeraporn Pinyakorn[1]; Frits van Griensven[1]; Eugene Kroon[1]; Naphassanant Laopraynak[1]; Robert O'Connell[2]; Nelson L. Michael[2]; Praphan Phanuphak[1]; Jintanat Ananworanich[2]; Nittaya Phanuphak[1]

[1]Thai Red Cross AIDS Research Center, Bangkok, Thailand; [2]US Military HIV Research Program, Bethesda, MD, US

Background: Syphilis has been reported to increase HIV viral load (VL) among HIV-infected persons and can cause genital ulceration, potentially increasing the risk for HIV transmission. Worldwide, syphilis rates among men who have sex with men (MSM) have been increasing.

Methods: We report syphilis prevalence and incidence in subjects enrolled during 2009-2014 in the RV254/SEARCH 010 cohort of acute HIV infection (AHI) in Bangkok, Thailand. VDRL is performed at baseline and every 48 weeks on all subjects, and in addition when clinically indicated. Positive results are confirmed with TPHA. CD4 testing, VL testing, clinical evaluation and HIV risk reduction counseling are performed every 12 weeks.

Results: Among 188 persons with AHI median age was 28 years, 95% were male and 91.5% were MSM. Syphilis prevalence at baseline was 6.9% (n=13). Median (inter-quartile range, IQR) time from HIV risk exposure to HIV diagnosis was 16 (12-21) days in syphilis cases and 19 (14-25) days in subjects without syphilis (p=0.02). Pre-antiretroviral treatment (ART) median HIV VL (log_{10} copies/ml) was 5.4 among syphilis cases and 5.8 among those without (p=0.04). Median (IQR) CD4 counts (cells/mm^3) were higher in those with syphilis at 534 (292-702) vs. 351 (257-481) (p=0.03).

Incident syphilis occurred in 17% (n=32). Overall incidence (per 100 person-years) was 11.5, rising from 0 in 2009 to 16.7 in 2012 and 12.0 in 2014 (p=0.66). Patients with syphilis had less education than those without (49% vs. 66% university education, respectively, p=0.04). Among 31 patients with incident syphilis who were on ART and had a VL test at the time of diagnosis, 30 had plasma VL below 50 copies/ml and one had VL of 323 copies/ml. Mean CD4 count (cells/mm^3) was 606 at the time of incident syphilis diagnosis, a decline from 627 pre-syphilis (p=0.42), and rebounded to 678 (p=0.01) post-syphilis treatment.

Conclusions: Syphilis is common among MSM in Bangkok at AHI diagnosis and during follow-up, with a rapid rise in incidence from 2009 to 2012. Baseline syphilis cases at AHI had higher CD4 counts and lower VL. Syphilis infection had no effect on HIV VL among those on ART but was associated with a transient and modest decline in CD4 count. Baseline and annual syphilis screening should be performed routinely on MSM with HIV infection in Thailand. Regular counseling must include the risk of sexually transmitted infections from oral sex or skin-to-skin contact in addition to anal or vaginal sex without condoms.

842 Serological Response to Treatment of Syphilis in HIV-Positive and HIV-Negative Adults

Rulin C. Hechter[1]; Robyn Neblett Fanfair[2]; W-L Joanie Chung[1]; Lauri E. Markowitz[2]; Sean S. Anand[1]

[1]Kaiser Permanente Southern California, Pasadena, CA, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: We assessed differences in serological response to syphilis treatment between HIV-positive (+) and HIV-negative (-) adults.

Methods: We performed a cohort study of adults diagnosed with incident syphilis in Kaiser Permanente Southern California from 2006 to 2012. Inclusion into the study required new positive syphilis serologies, documented syphilis treatment and at least one follow-up rapid plasma reagin (RPR) titer within 12 months from the date of syphilis diagnosis. We ascertained demographic and clinical characteristics through electronic medical records. Response to syphilis treatment within 12 months was assessed among a subset of subjects with baseline RPR titer ≥1:16.

Results: We identified 1062 HIV+ incident syphilis cases and 538 HIV- syphilis cases (Table 1). About 70% of the HIV+ cases were men who have sex with men. The median baseline RPR titer was 1:64 in HIV+ cases and 1:32 in HIV- cases; more HIV+ cases had a baseline RPR titer > 1:128 (20% vs. 8%). Among those with syphilis staging data, the majority of HIV- cases (51%) were diagnosed with a late latent syphilis, compared to only 8.4% of the HIV+ cases. Among HIV+ cases, 28% had a CD4 count ≤ 350 cells/mm^3 at syphilis diagnosis, and 73% had documented HAART use within 90 days of diagnosis. More HIV+ cases received benzathine penicillin G as the initial treatment of choice (91%) than HIV- cases (87%) (*P*=.006). Among those with a baseline RPR titer ≥1:16 (797 HIV+ and 339 HIV- cases), HIV+ cases had a lower rate of serologic failure (5%) within 12 months compared to HIV- cases (10%). HIV- cases who received doxycycline as the initial treatment had a higher treatment failure rate (14%) than those treated with benzathine penicillin G (9%) (*P*=0.36). Treatment failure rates were significantly (*P*=.003) greater among HIV+ cases diagnosed with latent syphilis (early: 6%, late: 16%, respectively) than those with primary (1%) or secondary syphilis (3%). Treatment failure was associated with a baseline RPR titer <1:32 only in HIV- cases (*P*=.007), but not in HIV+ cases.

Characteristic	HIV+ cases n=1062	HIV- cases n=538	Total N=1600
Age, median years (range)	43 (20, 81)	35.5 (18, 88)	42 (18, 88)
Male sex	1058 (99.6%)	423 (78.6%)	1481 (92.6%)
Race/ethnicity			
Black, non-Hispanic	184 (17.3%)	97 (18.0%)	281 (17.6%)
White, non-Hispanic	395 (37.2%)	120 (22.3%)	515 (32.2%)
Hispanic	390 (36.7%)	237 (44.0%)	627 (39.2%)
Asian/Pacific Islander	34 (3.2%)	39 (7.2%)	73 (4.6%)
Other/Unknown	59 (5.5%)	40 (7.4%)	99 (6.2%)
History of syphilis	574 (54.0%)	38 (7.1%)	612 (38.2%)
History of other STIs* within last 12 months	182 (17.1%)	6 (1.1%)	188 (11.8%)

*STI: history of a diagnosis of genital herpes, chlamydia, and/or gonorrhea within 12 months prior to the syphilis diagnosis.

Table 1. Baseline Characteristics of Incident Syphilis Cases by HIV Infection Status— Kaiser Permanente Southern California, 2006-2012

Conclusions: We found HIV- cases were more likely to experience treatment failure and had a lower baseline RPR titer compared to HIV+ syphilis cases. The association between a lower baseline RPR titer and treatment failure in HIV- cases warrants further investigations

TUESDAY, FEBRUARY 24, 2015

Session P-R7 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Opportunistic Infections: Odds and End Organs

843 The Exposure and Geospatial Risk Factors for AIDS-Associated Penicilliosis in Vietnam

Thuy Le[1]; Brian Jonat[2]; Ngo T. Cuc[3]; Nguyen T. Thanh[1]; Dang T. Bich[4]; Cecilia Shikuma[5]; Jeremy Day[1]; Heiman Wertheim[1]; Jeremy Farrar[1]; Marcel Wolbers[1]

[1]Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam; [2]New York-Presbyterian University Hospital of Columbia and Cornell, New York City, NY, US; [3]Hospital for Tropical Diseases, Ho Chi Minh City, Viet Nam; [4]National Hospital for Tropical Diseases, Hanoi, Viet Nam; [5]Hawaii Center for AIDS, University of Hawaii, Ho Chi Minh, Viet Nam

Background: Penicilliosis is an important opportunistic fungal infection in residents and travelers to Southeast Asia, China and India. Incidence increases during the rainy months and is associated with humidity and soil exposure. Bamboo rats are the only non-human host; however, evidence for zoonotic transmission is lacking, and disease reservoir and transmission risk remain unknown.

Methods: We conducted a case-control study to evaluate the exposure, behavioral, and geospatial risk factors for penicilliosis in 205 HIV-infected patients with incident penicilliosis and 406 control patients with AIDS but without pencilliosis. Cases and controls were matched for host susceptibility, which included age, sex, CD4 count or stage IV disease. Patients were recruited from the two largest referral centers for HIV care in northern and southern Vietnam. Conditional logistic regression analyses were used to evaluate the following risk categories for disease: injection drug use, antiretroviral therapy (ART), antifungal prophylaxis, cigarette smoking, outdoor occupation, proximity/exposure to bamboo rats, water, soil, tropical plants, highland plants, farming animals, domestic animals, and raw animal products. Geospatial risk was evaluated using global positioning mapping of patients' residence.

Results: 75% were male. Median age was 34 (IQR: 31 – 38) years. Median CD4 count was 16 (IQR: 7.0- 36.0) cells/μL. In the multivariate analysis, patients with proximity or occupational exposure to tropical plants (bamboo, sugar cane, and/or rice) and patients with occupational exposure to farming animals were at increased risk for penicilliosis, OR 1.84 (95% CI: 1.17-2.90), p=0.00841 and OR 2.03 (95% CI: 1.18-3.49), P=0.01007, respectively. In the univariate analysis, not being on ART, outdoor occupation, proximity/exposure to tropical plants, and exposure to farming animals were statistically significant risk factors for disease. Cases were geospatially distributed in southern Vietnam at provincial level. Comparing to controls, cases appeared to concentrate in the central highlands and its adjacent provinces north of Ho Chi Minh City.

Conclusions: Our data provided the first evidence for geospatial risk of penicilliosis in the endemic region. The identification of the highlands as disease hot spots suggested an ecological relationship between bamboo rats as an animal reservoir and a potential environmental reservoir in tropical plants and animal farming.

844 A5265 Clinical Trial: Gentian Violet for Oral Candidiasis is as Effective as Nystatin

Pranab K. Mukherjee[1]; Lauren Patton[2]; James Hakim[4]; Huichao Chen[3]; Mai T. Pho[5]; Kenneth A. Freedberg[6]; Caroline Shiboski[7]; Mahmoud A. Ghannoum[1]; Robert A. Salata[1]
Oral HIV/AIDS Research Alliance (OHARA)/ACTG

[1]Case Western Reserve University, Cleveland, OH, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]Harvard School of Public Health, Boston, MA, US; [4]University of Zimbabwe - Parirenyatwa, Harare, Zimbabwe; [5]University of Chicago, Chiago, IL, US; [6]Harvard Medical School, Boston, MA, US; [7]University of California San Francisco (UCSF), San Francisco, CA, US

Background: Oral candidiasis (OC) is a common infection in HIV-infected patients (HIVIP), especially in resource-limited settings (RLS), and is commonly treated with nystatin (NYS). We report the results of A5265, a randomized clinical trial (RCT) comparing the efficacy of gentian violet (GV) vs. NYS in the treatment of OC in HIVIP.

Methods: A5265 was a multicenter, open-label, assessment-blinded RCT in RLS sites to compare the safety & efficacy of topical GV to that of oral NYS suspension (enrollment target = 494 patients). Adult HIV-infected patients [stratified by CD4 cell counts (> or ≤200 cells/mm^3)] were randomized to receive either GV (0.00165%, BID) or NYS (500,000 units, QID) for 14 d. OC signs & symptoms were evaluated in a treatment-blinded manner. The study was stopped on 10/19/12 due to mortality unrelated to study drugs. 221 subjects were enrolled, and final results are presented. Primary endpoint: cure or improvement (reduction in severity ≥25%). Secondary endpoints (SEPs): cure, clinical improvement, symptoms (discomfort and pain), yeast colony counts, adverse events (AEs), tolerance, adherence, quality of life, acceptability, and cost per treatment course (CPTC). Repeated confidence intervals (CIs) were used to control type I error of 0.05 (99.7% and 95.1% CI for interim and final analyses, respectively).

Results: 202 patients were eligible for analysis (GV, n=100; NYS, n=102). 76 (76%) in the GV arm had cure or improvement of OC compared to 73 (71.6%) in the NYS arm, resulting in a non-significant (NS) difference in clinical efficacy rates (GV-NYS) of 0.044 (CI = -0.077, 0.166). Efficacy of GV was significantly higher than that of NYS when stratified by CD4 count (>200 cells/mL; CI = 0.02, 0.36). No GV-related AEs were noted. Pain was significantly lower in GV than in NYS arm at relapse ($P = 0.03$). 61% and 39% of participants in GV arm had no or mild-to-moderate staining, respectively. No significant difference was found between the two arms in efficacy rates or any other SEPs. CPTC of GV ranged from US $0.38 to $3.15, while that of NYS ranged from $6.25 to $37.48. The NS results could be due to lower enrollment. However, within the reduced sample size limitation of the study, the results were in favor of GV.

Conclusions: We found that GV is as effective as, and less costly than, NYS in the treatment of OC in the HIV-setting, and may thus provide an inexpensive alternative in RLS countries.

845 Effective Treatment of Lymphogranuloma Venereum (LGV) With 1g Azithromycin Administered Weekly for 3 Weeks in an HIV-Infected Population

José L. Blanco; Irene Fuertes; Jordi Bosch; Ana Gonzalez; Andrea Vergara; Rob Camp; Esteban Martinez; Teresa Estrach; Josep M. Gatell; Merçe Alsina

Hospital Clinic, Barcelona, Barcelona, Spain

Background: Lymphogranuloma venereum (LGV) is an ulcerative and invasive sexually transmitted disease (STD) caused by Chlamydia trachomatis Serovar L1, L2, or L3. LGV has become hyperendemic among men who have sex with men (MSM) in Western Europe. Doxycycline (100 mg orally twice daily for 3 weeks, DoxLGV) has long been the regimen of choice because there are no controlled trials supporting alternative treatments. Even though azithromycin (1 g orally once weekly for 3 weeks, prolonged azithromycin regimen, PAzR) is likely to be effective against LGV, limited data are available on the clinical effectiveness of this antibiotic in the treatment of LGV. We aimed to evaluate treatment with oral PAzR in patients presenting with rectal LGV infection.

Methods: A longitudinal prospective study at the STD Unit in the Hospital Clinic was conducted in Barcelona between 6/2010 and 4/2014. Adult patients were eligible for inclusion if they presented with clinical manifestation of anorectal syndrome or any clinical suspicion of LGV infection after recent history of unsafe sex. All patients received a single dose of 1 gr intramuscular ceftriaxone but were aleatorily assigned to receive, If LGV was detected, at visit 1 (day +7): (i) oral doxycycline 100 mg twice a day for 3 weeks; or (ii) azithromycin 1 g orally once weekly for 3 weeks. All participants were clinically assessed and those in the PAzR group were also assessed weekly by real-time multiplex polymerase chain reaction (M-PCR) that includes LGV (visit 2, day +14; visit 3, day +21; visit 4/end of study, day +28).

Results: 60 patients were included (28 doxycycline, 32 PAzR), all MSM, 95% HIV-positive, 85% receiving ART, 75% showing plasma HIV RNA below detection, 25% simultaneously diagnosed with other STDs. Average time between onset of symptoms and diagnosis was 39 days (1-180). Two patients in the DoxLGV group and one in PAzR were lost to follow-up. Patients who correctly completed doxycycline (n=27, 96%) and PAzR (n=30, 94%) all clinically responded. All patients but one in the PAzR group became negative for the M-PCR-LGV during the regimen. The one asymptomatic patient with persistent M-PCR for LGV at day +28 became negative after DoxLGV treatment. No treatment-related adverse events were reported.

Conclusions: Our findings show that an extended but simple azithromycin regimen (PAzR) was as effective as standard doxycycline (DoxLGV) and may be considered for successful treatment of LGV in an HIV-infected population.

846 Risk Factors for Staphylococcus Aureus Carriage in HIV-Infected Adults in Southern Botswana

Michael J. Reid[1]; **Rebceca Fischer**[3]; Naledi Mannathoko[2]; Eric Brown[3]; Andrew Steenhoff[4]

[1]University of California San Francisco, San Francisco, CA, US; [2]University of Botswana, School of Medicine, Gaborone, Botswana; [3]University of Texas, Texas, Afghanistan; [4]University of Pennsylvania, Gaborone, Botswana

Background: Despite the huge burden of HIV disease, data describing the prevalence of Staphylococcus aureus nasal carriage in the setting of HIV infection in southern Africa are sparse.

Methods: This cross-sectional study sought to estimate the prevalence of S. aureus nasal carriage and define risk factors for colonization among HIV-infected individuals in southern Botswana. 418 HIV-infected individuals (116 men, 302 women) were screened twice for nasal carriage of methicillin-susceptible (MSSA) and methicillin resistant (MRSA) S. aureus over a 4-week interval at two outpatient facilities. S. aureus carriage was further defined as either intermittent (carriage at one visit but not both) or persistent (carriage at both visits). Nasal carriage was related to demographic characteristics, HIV parameters, co-morbidities, and exposure to health care services.

Results: Prevalence of nasal colonization for S. aureus was 38% (n=158); 49% (n=78) were intermittent carriers, 51% (n=80) persistent carriers. Prevalence of intermittent MRSA carriage was 3% (n=13); no patients were persistently colonized by MRSA. Those > 18 years were less likely to be persistent carriers than those < 18 years (Prevalence Ratio [PR] 0.41, p=0.003). Those accessing care at a semi-rural facility (PR 2.19, p=0.005), sharing households with ≥1 child (PR 1.36, p=0.06) and those with elevated viral loads (>399 copies/mL) (PR 1.88, P=0.019) were also more likely to be persistent carriers than non-carriers.

Those with MRSA were more likely to be <18 years old (PR 0.12, p<0.05) and have history of eczema (PR 5.72, p=0.001), asthma (PR 3.75, p<0.05), tuberculosis (PR 3.26, p=0.03), or pneumonia (PR 3.6, p=0.03). Neither MSSA nor MRSA was significantly associated with viral load or CD4 count. However, MRSA was more prevalent than MSSA among those on third line (PR 4.52, p=0.08) antiretroviral regimes and those with detectable viral loads (PR 1.67, p=0.052).

Conclusions: HIV-infected children, persistent viremia and those living in semi-rural and larger households constitute high-risk groups for nasal carriage for S. aureus. Intermittent MRSA carriage was more prevalent among younger patients with unsuppressed viremia and co-morbid diseases. Persistent nasal MRSA colonization among non-hospitalized HIV-infected persons was neglible

847 Specific Behaviors Predict *Staphylococcus aureus* Colonization and Skin and Soft Tissue Infections Among HIV-Infected Persons

Nancy Crum-Cianflone; Xun Wang; Amy Weintrob; Tahaniyat Lalani; Mary Bavaro; Katrin Mende; Michael Ellis; Brian K. Agan

Infectious Disease Clinical Research Program, San Diego, CA, US

Background: *Staphylococcus aureus* skin and soft tissue infections (SSTIs) have markedly increased over the past two decades. Few prospective data exist on the incidence rates and risk factors of *S. aureus* colonization and SSTIs among HIV-infected persons in the HAART era.

Methods: We screened 516 HIV-infected adults at three geographically diverse locations. *S. aureus* colonization was examined at five specific body sites (nares, throat, axilla, perirectal and groin). After excluding those colonized at baseline (n=161) or lost to follow-up (n=33), 322 participants were prospectively evaluated over a 2-year period for incident colonization and SSTIs. Study visits occurred every 6 months and included multiple sociodemographic, behavioral, clinical, and laboratory measures. Separate Cox proportional hazard models with time-updated covariates assessed the predictors of *S.aureus* colonization and SSTIs.

Results: 322 participants had a median age of 42 years (IQR 32-49), median duration of HIV of 9.4 years (2.7-17.4), and 58% were receiving HAART. Overall, 102 (32%) became colonized with *S. aureus* with an incidence rate of 206 (95% CI 168-250) per 1000 PYs. Predictors of *S. aureus* colonization in the final multivariate model included illicit drug use (HR 4.26, 95% CI 1.33-13.69) and public gym use (HR 1.66, 95% CI 1.04-2.66), while antibacterial soap use was protective (HR 0.5, 95% CI 0.32-0.78). Overall, 14% developed an SSTI [incidence rate of 94 cases (95% CI 68-127)/1000 PYs]. Risk factors for developing an SSTI in the time-updated unadjusted Cox models included incident *S. aureus* colonization, illicit drug use, tattoo receipt, public shower use, public gym use, and hospitalization in the last six months. In the final multivariate model, *S. aureus* colonization (HR 2.52, 95% CI 1.35-4.69), public shower use (HR 2.59, 95% CI 1.48-4.56), and hospitalization in the last six months (HR 3.54, 95% CI 1.67-7.53) predicted SSTIs. HIV-related factors (history of AIDS, CD4 count, viral load, and HAART use), sexual behaviors, and owning a pet were not predictive of incident colonization or SSTIs.

Conclusions: HIV-infected adults have a high incidence of *S. aureus* colonization and SSTIs. Specific behaviors, but not HIV-related factors, were predictors of colonization and SSTIs in our study. These data suggest that behavioral modifications may be the most important strategies in preventing *S. aureus* colonization and SSTIs among HIV-infected persons.

848 Cytokine Profile in Aqueous Humor of HIV Patients With Ocular Opportunistic Infections

Matilde Ruiz-Cruz; Santiago Avila-Rios; Christopher Ormsby; Claudia Alvarado-de la Barrera; Yuria Ablanedo-Terrazas; Gustavo Reyes-Terán

National Institute of Respiratory Diseases, Mexico City, Mexico

Background: Opportunistic ocular infections (OI) are commonly associated with HIV infection. Immunologic factor profiles in aqueous humor (AqH) in different OI in the context of HIV infection are yet to be elucidated. We determined the cytokine and chemokine profiles in AqH and plasma of HIV-infected individuals with OI, before and after specific treatment.

Methods: OI diagnoses and post-treatment assessments were performed in 46 HIV-infected individuals, including 23 patients with cytomegalovirus retinitis (CMVr), 16 with ocular syphilis and 7 with other OI. As control groups, plasma from 15 healthy donors and AqH from 16 patients undergoing cataract surgery were included. Concentrations of 27 cytokines in AqH and plasma before and after OI treatment were assessed using a multiplex assay. Cytokine concentrations in AqH and plasma were compared between different OI and between HIV-infected individuals and controls, using Wilcoxon tests corrected for multiple comparisons. Statistical analysis was carried out using R software version 3.0.2

Results: Characteristic cytokine profiles were observed in AqH of CMVr and ocular syphilis with higher levels of GM-CSF, IL-1α and IP-10 in CMVr ($p<0.03$). After treatment of CMVr, a significant reduction in the concentration of AqH proinflammatory cytokines (IFN-2α, IL1α, IL-6, TNFα, and IFN-γ; $p<0.003$), chemokines (eotaxin, IL-8, MCP-1, MIP-1α, MIP-1β, and IP-10; $p<0.0005$), and growth factors (G-CSF and GM-CSF; $p<0.0001$) was observed. Additionally, a significant reduction ($p<0.002$) in IL-10 plasma concentrations was observed. After treatment of ocular syphilis, we observed a significant reduction in AqH concentrations of proinflammatory cytokines (IL-1α and IL-6; $p<0.014$), chemokines

(eotaxin, IL-8, IP-10, MCP-1, and MIP-1α; $p<0.005$), and growth factors (G-CSF and GM-CSF; $p<0.001$). We also found a significant reduction in plasma concentrations of IFN-2α($p<0.014$).

Conclusions: We found that reductions in levels of several cytokines and chemokines in patients with CMVr and ocular syphilis after specific treatment are associated with clinical improvement, consistent with the control of a Th1 inflammatory milieu. Knowledge on specific immunologic profiles in different OI could support diagnosis and disease prognosis, as well as the individualization of intraocular treatment in the future, focusing on the reduction of specific cytokines.

849 Effects of *H. pylori* Co-infection on Immune Parameters in HIV-1 Patients in Ghana

Edmund Osei-Kuffour[1]; Torsten Feldt[1]; Kirsten A. Eberhardt[2]; Fred S. Sarfo[4]; Marieke Soltau[2]; Jan F. Drexler[3]; Gerd D. Burchard[2]; Carsten Münk[1]; Dieter Häussinger[1]
HHECO Study Group

[1]University Clinic Düsseldorf, Heinrich-Heine-University, Düsseldorf, Germany; [2]Bernhard-Nocht-Institute for Tropical Medicine, Hamburg, Hamburg, Germany; [3]University of Bonn, Bonn, Germany; [4]Kwame Nkrumah University of Science and Technology, Komfo Anokye Teaching Hospital, Kumasi, Ghana

Background: Worldwide, there is a high co-endemicity of HIV and *H. pylori* infection. The objective of this study was to investigate the effects of *H. pylori* infection on clinical, immunological and virological parameters in HIV-positive individuals in Ghana and uninfected controls in Ghana.

Methods: Cross-sectional, observational study. Consecutive HIV-patients and HIV-negative blood donors were recruited at a university hospital in Kumasi, Ghana. *H. pylori* status was tested using a stool antigen test. Clinical and sociodemographic parameters, CD4 cell count, HIV-1 viral load were analysed. In addition, markers for T-cell activation and regulation were quantified by flow cytometry. Parameters were compared according to HIV- and *H. pylori* status (see table 1 for statistical tests). The study was registered at Clinicaltrials.gov (NCT01897909). Recruitment for this has been completed, follow-up is currently on-going.

Results: The prevalence of *H. pylori* infection was significantly lower in HIV-infected (n=942) compared to HIV-negative (n=100) adults in Ghana (51.5% vs. 88%, p<0.0001). ART naïve HIV-patients (but not those on ART) with *H. pylori* co-infection (n=239) had higher CD4 cell counts (312 vs. 189 cells/µl, p<0.0001) and lower HIV-1 viral loads (4.92 vs. 5.21 log10 copies/ml, p=0.006) compared to those without *H. pylori* co-infection (n=255). In those patients, we also found lower proportions of CD4 T-cells with markers of immune activation (CD4+CD38+HLA-DR+; 22.55 vs 32.7, p=0.002), cell proliferation (CD4+Ki67+; 13.7 vs 25.3, p= 0.02) and immune exhaustion (CD4+PD-1+; 32.45 vs 40.00, p=0.005). PBMC for flow cytometry analysis were available for 243 of 494 ART- naïve patients (see table 1). H. *pylori* infection was not associated to more frequent gastrointestinal symptoms, anaemia or lower BMI. Having no access to pipe-borne water and higher CD4 cell counts were identified as risk factors for *H. pylori* infection. The use of antibiotics, including co-trimoxazole prophylaxis, was not associated with *H. pylori* co-infection.

Comparison of demographic, clinical and laboratory parameters in HIV-infected individuals according to *H. pylori* status

Variable	H. pylori co-infected group	H. pylori negative group	p-value
HIV-infected, all patients, n=942	**n=490 (52.0%)**	**n= 452 (48.0%)**	
Female gender, n (%)	372 (75.9)	339 (75.0)	0.74
Mean ± SD age (years)	40 ± 9.4	40 ± 9.6	0.97
Access to pipe-borne water, n (%)	239 (48.8)	262 (58.0)	0.005
HIV-infected, ART-Naïve group, n=494	**n=239 (48.4%)**	**n=255 (51.6%)**	
BMI	22.4 ± 4.1	21.9 ± 4.2	0.19
On tuberculosis treatment, n (%)	21 (8.8)	41 (16.1)	0.01
Antibiotic use in past six months, n (%)	3 (1.3)	2 (0.8)	0.68
Use of co-trimoxazole, n (%)	62 (25.9)	80 (31.4)	0.18
Median (IQR) log 10 viral load/ml	4.92 (4.09-5.51)	5.21 (4.59-5.63)	0.006
Median (IQR) CD4 T-cell count/µl	312 (128 – 508)	189 (75-403)	<0.0001
Median (IQR) CD38+HLA-DR+(%CD4+)	22.55 (0.00 - 82.90)	32.7 (3.45 - 77.80)	0.0021
Median (IQR) Ki-67+(%CD4+)	13.7 (3.07 - 78.30)	25.3 (2.71-79.20)	0.0193
Median (IQR) PD-1+(%CD4+)	32.45 (0.00 - 94.40)	40 (8.47- 88.20)	0.0051
HIV-infected, ART- treatment group,n=448	**n=251 (56.0%)**	**n=197 (44.0%)**	
BMI	24.3 ± 4.5	23.8 ± 4.6	0.21
On tuberculosis treatment, n (%)	1 (0.4)	2 (1.0)	0.58
Antibiotic use in past six months	0 (0.0)	1 (O.5)	0.58
Use of co-trimoxazole	49 (19.5)	48 (24.4)	0.25
Median (IQR) log 10 viral load/ml	3.67 (3.10-4.57)	3.09 (2.31-4.71)	0.54
Median (IQR) CD4 T-cell count/µl	450 (270 - 643)	476 (272 – 654)	0.78
Median (IQR) CD38+HLA-DR+(%CD4+)	12.9 (2.71 - 47.90),	11.9 (2.91-46.40)	0.6829
Median (IQR) Ki-67+(%CD4+)	7.75 (3.03-32.20)	8.9 (2.25-30.60)	0.1898
Median (IQR) PD-1+(%CD4+)	31.8 (2.99-80.70)	31.7 (6.54-90.30)	0.8421
HIV-uninfected controls, n=100	**n=88 (88.0%)**	**n= 12 (12.0%)**	<0.0001
Female gender, n (%)	57 (66.3)	9 (75.0)	0.304
Mean ± SD age (years)	32.92 ± 12.2	31.58 ± 13.0	0.726
Median (IQR) CD4 count Cells/ml	977 (337-2429)	854(524-1923)	0.297
Median (IQR) CD8 Count cells/ml	436 (18-1337)	529.5(50-1275)	0.27

Conclusions: HIV-infection was associated with a clearly lower rate of *H. pylori* co-infection. In ART-naïve HIV-patients, *H. pylori* co-infection was associated with higher CD4 cell counts, lower HIV-1 viral loads and decreased markers of CD4 T-cell activation and exhaustion. Effects of *H. pylori* infection on systemic immune activation, as key factor in HIV pathogenesis, and on HIV disease progression warrant further investigation.

THURSDAY, FEBRUARY 26, 2015

Session P-S1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Access and Engagement

850 Trends in Healthcare Access and HIV Risk Behaviors—African American Women, 2006-2013

Wade Ivy; Gabriela Paz-Bailey

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: In 2010, African American women accounted for 29% of the estimated new HIV infections among adult and adolescent African Americans in the US, a 21% decrease since 2008. The factors that contributed to this decrease are unknown; however, we hypothesized that improvements in healthcare access and socioeconomic factors may have contributed to this reduction.

Methods: We analyzed data from three cycles of the National HIV Behavioral Surveillance system (2006, 2010, and 2013). Heterosexuals of low socioeconomic status or who were residents of census tracts with high rates of poverty were surveyed from over 20 US cities with high prevalence of AIDS using respondent-driven sampling and venue-based sampling, and asked to complete an HIV test. We analyzed data from African American women living at or below the poverty threshold using GEE to determine differences in access to healthcare and risk behaviors over time, controlling for education and city of residence. Models were run separately using each of the variables under investigation as outcomes.

Results: Data from 11,065 African American women were analyzed. Significant increases were found in the percentage of women who reported ever having an HIV test (78%, 84% and 89%, in 2006, 2010 and 2013, respectively; $p<0.001$), having current health insurance (60%, 65% and 74%, respectively; $p<0.001$), and recently (past 12 months) visiting a healthcare provider (74%, 77% and 84%, respectively; $p<0.001$). The percentage of women who reported being unemployed decreased (47%, 47% to 41%, respectively, $p<0.001$), as did those reporting an annual income of less than $10,000 (73%, 75% and 63%, respectively, $p<0.001$), and those reporting recent injection drug use (6%, 3% and 3%; $p<0.001$). However, behaviors that facilitate HIV transmission increased from 2006 to 2013. The percentage of women who reported condomless vaginal sex at last sex (78%, 81% and 83%; $p<0.001$), condomless anal sex at last sex (8%, 13% and 32%; $p<0.001$), or 3 or more sex partners in the past 12 months (41%, 46% and 46%; $p<0.001$) increased significantly over time.

Conclusions: From 2006 to 2013, improvements in access to healthcare, HIV testing, and socioeconomic factors and reductions in injection drug use were reported by African American women. However, the percentage of women reporting high-risk sexual behaviors increased over time. More research is needed to understand the factors that contribute to the recent decline in new HIV infections among African American women.

851 Engagement in the HIV Care Continuum Among Female Sex Workers in Lilongwe, Malawi

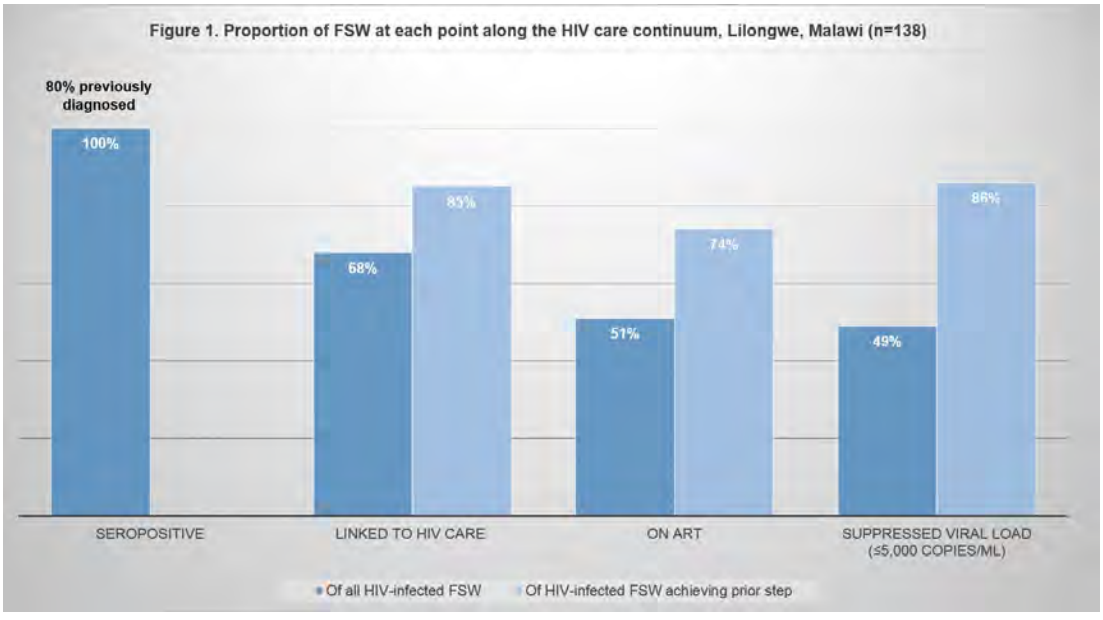
Kathryn E. Lancaster[1]; Thandie Lungu[3]; Mina C. Hosseinipour[3]; Katy Chadwick[2]; Zoe Dibb[2]; Vivian F. Go[1]; Brian W. Pence[1]; Kimberly A. Powers[1]; Irving F. Hoffman[1]; William C. Miller[1]

[1]University of North Carolina, Chapel Hill, NC, US; [2]Theatre for a Change, Lilongwe, Malawi; [3]University of North Carolina Project–Malawi, Lilongwe, Malawi

Background: Female sex workers (FSW) are a key population at great risk for HIV acquisition and transmission within the generalized epidemics of sub-Saharan Africa. This study documents FSW engagement in the HIV care continuum in Lilongwe, Malawi, where the HIV prevalence among FSW is among the highest globally.

Methods: In July and August 2014, we recruited 200 FSW in Lilongwe, Malawi using venue-based sampling. FSW who were ≥18 years and reported receiving money in exchange for sex in the past 12 months participated in a biological and behavioral survey to assess their engagement in the HIV care continuum. Seropositive FSW, identified using HIV rapid testing, received PIMA CD4 counts and HIV-1 RNA levels using dried blood spots. We estimated proportions for HV seroprevalence, previous HIV diagnosis (self-report), linkage to HIV care (self-report of ever having seen an HIV care provider), current ART status (self-report), and viral load suppression (≤5000 copies/ml).

Results: HIV seroprevalence was 69% (n=138). Of all the HIV-infected FSW, 20% (Figure 1) were newly diagnosed (n=20 (15%) previously tested negative; n=7 (5%) never tested or never received results). Among newly diagnosed FSW that previously tested negative, the median time since last HIV test was 11 months (IQR: 3-17). The median CD4 among all newly diagnosed FSW was 464 cells/mm^3 (IQR: 276-632). 85% of previously HIV-diagnosed FSW reported linkage to care, representing 68% of all HIV-infected FSW. Among all HIV-infected FSW, 49% were not on ART with a median CD4 of 478 cells/mm^3 (IQR: 321-656). 74% of previously diagnosed and linked to care FSW were currently receiving ART, representing 51% of all HIV-infected FSW. Among the 51% of all HIV-infected FSW on ART, 86% (n=60) were virally suppressed and 67% (n=48) reported never skipping pills within the prior month.



Conclusions: FSW in Lilongwe have high HIV prevalence and proportion of newly diagnosed HIV infections, with a substantial proportion of HIV-infected FSW experiencing inadequate engagement in the HIV care continuum. Although the majority of FSW who are on ART are virally suppressed, ART uptake and adherence are sub-optimal. To reduce ongoing transmission and improve health outcomes, increased FSW engagement in the HIV care continuum is urgently needed. Incorporation of universal testing and treatment strategies for all FSW in Malawi must be strongly considered.

852 New HIV Cases and ARV Retention in Pretoria: A Gender Project for High-Risk Women

Wendee M. Wechsberg[1]; William A. Zule[1]; Irene A. Doherty[1]; Tracy L. Kline[1]; Jacqueline Ndirangu[1]; Charles M. van der Horst[2]
[1]RTI International, Research Triangle Park, NC, US; [2]University of North Carolina, Chapel Hill, NC, US

Background: HIV testing and treatment programs by the South African Government currently miss many drug using women and sex workers. Retention rates in antiretroviral therapy (ART) for women who test positive are poor. This presentation reports complete baseline data regarding the HIV treatment cascade from women enrolled in a gender-focused NIDA-funded cluster randomized study in Pretoria, South Africa to increase HIV testing, treatment and retention in ART.

Methods: We used natural boundaries (e.g. highways, rivers, etc.) to divide the city of Pretoria (635 sq. miles) into 14 zones. Outreach workers for the project recruited sex workers and other women who reported using alcohol or drugs at least weekly from all 14 zones. We enrolled 640 women who completed interviews, testing for HIV, pregnancy, and recent alcohol and drug use.

Results: The most common biologically confirmed drugs of abuse were marijuana 32%, opiates 18%, and cocaine 15%, and 14% had a positive alcohol breathlyzer. HIV prevalence was 55% overall, and 68% among sex workers. Eleven percent of women reported this was their first HIV test. Of these, 52% of were newly diagnosed with HIV. Of the women who had been tested previously, 85 (15%) were newly diagnosed. Only 22% of HIV positive women were on ART. CD4 counts results were only available for 39%. Of women with a CD4 count, 36% had a count ≤350 which made them eligible for ART, but only 37% of them were on ART. The major ART were structural (e.g. clinics far away, clinics ran out of ARVs, no CD4 tests, etc.) and individual barriers (e.g. food insecurity, belief in traditional medicine, addiction).

Conclusions: More people live with HIV in South Africa than anywhere else in the world. Yet, there is still an unmet need for reaching, testing, treating and retaining high risk HIV positive women. South Africa must increase focused efforts for high risk groups to help them progress successfully through the HIV treatment cascade. This project is testing a woman-focused intervention to help HIV positive progress through the treatment cascade and achieve suppressed viral loads.

853 Intimate Partner Violence and Antiretroviral Adherence in HIV-Positive Women in Kenya

Kate S. Wilson[1]; Krista Yuhas[1]; Ruth Deya[1]; Barbra Richardson[1]; Linnet Masese[1]; Jane Simoni[1]; Walter Jaoko[2]; R Scott McClelland[1]
[1]University of Washington, Seattle, WA, US; [2]University of Nairobi, Nairobi, Kenya

Background: Intimate partner violence (IPV) is common in HIV-positive women and may be a risk factor for poor adherence. We examined whether recent IPV was associated with poor antiretroviral therapy (ART) adherence among HIV-positive women in Mombasa, Kenya, who reported trading sex for cash or in-kind payment.

Methods: Women in our prospective cohort study were HIV-positive, ≥18 years, eligible for ART and reported transactional sex. Women completed monthly follow-up visits and were offered HIV care including ART according to Kenyan guidelines. Intimate partner violence in the past year was defined as experiencing ≥1 of 13 acts of physical, sexual, or emotional violence by the current or most recent regular partner (index partner). Exposure to IPV was updated yearly. Poor adherence was defined as >48 hours late for a scheduled monthly ART refill by clinic data. We have previously shown that late refill is associated with plasma and genital HIV detection and genotypic HIV resistance. Adherence in the past month using a validated self-rating scale (very good/excellent vs. less than very good) and visual analogue scale (VAS) <80% were secondary endpoints. We used generalized estimating equations with a log link, exchangeable correlation structure, and robust standard errors to estimate relative risks (RR) and 95% confidence intervals (CI). Models were adjusted for age and education.

Results: Overall, 247 women contributed 315.5 person-years to the analysis. Median age was 40 years (interquartile range [IQR] 35-45). Of 3,835 total visits, 568 (14.8%) were contributed by women who reported IPV by their index partner in the past year. Of 3,172 visits with refill data, late refill occurred at 86/480 (17.9%) IPV exposed and 693/2,692 (25.7%) IPV unexposed visits (RR 0.89, 95% CI 0.74, 1.08). The adjusted association was similar (aRR 0.85, 95% CI 0.69, 1.04). Results were similar when visits where women refused or had stopped ART were excluded, and when analyses were restricted to visits with an index partner. There was also no evidence that IPV was associated with increased risk of poor adherence by self-rating scale (data not shown).

Conclusions: Intimate partner violence was common in this cohort of high-risk HIV-positive Kenyan women. However, we found no evidence that IPV was associated with poor ART adherence. While IPV should be addressed as an important women's health problem, we may not expect reductions in IPV to be associated with improved ART adherence.

854 Re-engagement in Care Leads to Sustained Engagement and Viral Suppression

Brittani D. Saafir-Callaway[1]; Amanda D. Castel[2]; Lena Lago[1]; Christie Olejemeh[1]; Garret Lum[1]; Lawrence Frison[1]; Michael Kharfen[1]
[1]District of Columbia Department of Health, Washington, DC, US; [2]The Milken Institute School of Public Health at George Washington University, Washington, DC, US

Background: The HIV Care Continuum requires HIV+ people to be fully engaged in HIV care and treatment in order to achieve viral suppression. However, many people cycle in and out of care making it difficult for them to achieve this goal. We sought to use HIV surveillance and clinical data to determine whether identification and subsequent re-engagement of HIV+ out of care people results in improved retention in care and clinical outcomes.

Methods: Through the District of Columbia Department of Health (DC DOH) Recapture Blitz, data on 1,015 HIV+ persons were received from 7 clinical providers who identified persons as being out of care for a 12-month period. Persons were matched to the DC DOH surveillance and services databases, and those without evidence of receipt of care based on surveillance data were sent back to clinics for investigation. Median CD4 and viral load, retention in care, and viral suppression at last lab after re-engagement were assessed 12 months following the Recapture Blitz.

Results: From October 2012 to April 2013, 691 HIV+ persons had no evidence of being in care and were subsequently investigated. Viral load or CD4 results were available for 390 (56%) of those investigated. At their last known lab, the median viral load and CD4 among out of care persons was 200 copies/ml and 27 cells/μl, respectively. Of the 691 persons investigated, 573 (83%) were contacted for re-engagement: 121 (21%) were in care elsewhere, 61 (11%) had moved to another jurisdiction, and 59 (10%) were re-engaged in care. As of April 2014, the majority of re-engaged persons remained in care (n=44, 75%); 32 (54%) were retained in continuous care and 12 (20%) were sporadically engaged in care. Fifteen people (26%) had no evidence of being in care as per surveillance records. Among persons retained in care at 12 months of follow-up, 25 (57%) were virally suppressed at their last reported viral load. The median CD4 results among persons retained in care increased significantly from 26 cells/μl at last known lab to 458 cells/μl after 12 months of follow-up (p<.0001) while the median viral load decreased from 1,800 to 85 copies/ml (p=0.1665).

Conclusions: Through the Recapture Blitz, using a combination of surveillance and clinical data allowed not only for successful re-engagement in care but resulted in improved longer term health outcomes post-re-engagement. This analysis underscores the importance of re-engaging persons who have fallen out of care to improve overall rates of retention and viral suppression.

TUESDAY, FEBRUARY 24, 2015

Session P-S2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Cervical Sampling, Shedding, and Outcomes

855 Symptoms and Genital HSV-2 and HIV-1 in Coinfected Women, Chiang Rai, Thailand

Eileen F. Dunne[1]; Brooke E. Hoots[1]; Janet McNicholl[1]; Sara Whitehead[2]; Thomas A. Peterman[2]; Lauri E. Markowitz[2]; Wanna Leelawiwat[3]; Tammy Evans-Strickfaden[1]; Cheng Chen[1]

[1]US Centers for Disease Control and Prevention, Bangkok, Thailand; [2]US Centers for Disease Control and Prevention, Atlanta, GA, US; [3]Thailand Ministry of Public Health–US CDC Collaboration, Nonthaburi, Thailand

Background: There are few studies examining daily HIV-1 and HSV-2 shedding in HIV-1 and HSV-2 co-infected women. We examined the association between daily genital HSV symptoms and daily HSV-2 and HIV-1 genital shedding.

Methods: Sixty-seven Thai women participating in the placebo arm of a randomized, crossover placebo-controlled trial of the effect of acyclovir on HIV-1 shedding provided daily information on genital symptoms (genital sores and other symptoms self-reported on daily diary cards). Eligible women were aged 18–49 years, had regular or no menses, had serum antibodies to HSV-2 and HIV-1, and were not eligible for antiretroviral therapy by Thai national guidelines at the time. Women self-collected genital swabs of the vaginal, vulvar and perianal region, inserted the swabs into a sponge with DNA/RNA preservative, and kept the tubes in a cooler until weekly collection. Nucleic acid extraction of both HIV-1 RNA and HSV-2 DNA were conducted and specimens with detectable virus were quantified. Associations between shedding and patient characteristics were evaluated using binomial regression with generalized estimating equations with an exchangeable correlation matrix to account for non-independence of swabs collected from the same woman.

Results: During the study, 20 (30%) participants reported burning, itching, tingling, or pain in any area on at least one day and 23 (35%) reported a sore on at least one day during the month. Of 561 swabs tested for HSV-2 DNA, 27% had detectable virus and of 525 swabs tested for HIV-1 RNA, 71% had detectable virus. Most shedding occurred in the absence of sores or symptoms (77% of swabs with detectable HSV-2 and 86% of swabs with detectable HIV-1). However, compared to swabs from women with no symptoms or sores, swabs from women with symptoms in the three-day window before collection were 2.0 (95% CI: 1.2-3.3) times as likely to be positive for HSV-2 DNA, and swabs from women with sores were 2.7 (95% CI: 1.6-4.4) times as likely to be positive. Neither symptoms nor sores reported in a three-day window prior to swab collection were associated with HIV shedding.

Conclusions: While HSV-2 shedding was more likely to occur following symptoms and sores, HIV-1 shedding was not; this difference in shedding suggests that HIV-1 shedding may be unrelated to HSV-2 mediated mucosal events. Our study found that most HSV-2 as well as HIV-1 genital shedding occurred primarily during days when there were no clinical symptoms.

856 High-Risk HPV Clustering and Cervical Outcomes in HIV-Infected Women in Rio de Janeiro, Brazil

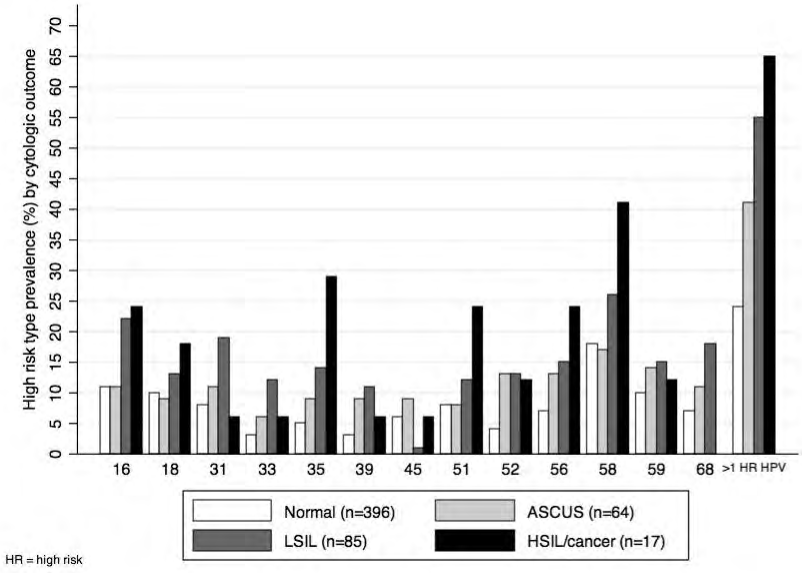
Jessica L. Castilho[1]; José Eduardo Levi[2]; Paula M. Luz[2]; Mary Catherine Cambou[3]; Tazio Vanni[4]; Angela de Andrade[2]; Monica Derrico[2]; Valdilea Veloso[2]; Beatriz Grinsztejn[2]; Ruth Friedman[2]

[1]Vanderbilt University School of Medicine, Nashville, TN, US; [2]Fundação Oswaldo Cruz, Rio de Janeiro, Brazil; [3]University of California Los Angeles, Los Angeles, CA, US; [4]United Nations, Lyons, France

Background: In Brazil, rates of HPV infection and cervical cancer remain high. With ongoing vaccine development, information of specific HPV type prevalence, particularly among HIV-infected women, is needed.

Methods: We performed a cross-sectional study of HIV-infected women in Rio de Janeiro, Brazil, who underwent cervical HPV genotype testing between 2006-2013. We examined the prevalence of HPV types and the patterns of high risk HPV type clustering. Using logarithmic binomial regression, we estimated the risk of abnormal cytology by HPV genotype result, adjusting for patient factors.

Results: Of the 562 women included, 364 women (65%) had at least one high risk HPV type detected, and 181 (32%) had more than one high risk type detected. Overall, HPV 58 was the most frequent HPV type detected (prevalence 19.8% [95% confidence interval 16.4-23.1]); HPV 16 was the second most frequent high risk type (prevalence 13% [10.2-15.8]). Prevalence of high risk HPV types by cytology outcome are shown in the Figure. Women infected with more than one high risk HPV type were younger, had lower CD4+ lymphocyte counts, were more likely to be infected with HPV 16 or 18, and were more likely to have abnormal cytology. There was no difference in duration of antiretroviral therapy by HPV genotype result. Among women with abnormal cytology, individual high risk HPV clustering patterns were diverse and without a predominant high risk pair (the most frequent pair, HPV 31 and 58, occurred in only 6% of cases). While many high risk HPV types were associated with abnormal cytology in univariate analyses, none remained statistically significant in models adjusting for presence of more than one high risk type, age, and CD4+ lymphocyte count. In multivariate models, presence of more than one high risk type was associated with a two-fold increased risk of abnormal cytology in every model (adjusted prevalence ratios [aPRs] 1.88-2.07, all p values <0.001). CD4+ lymphocyte count also remained statistically significant in every model (aPRs 0.91-0.92 per 100 cells/mL increase, all p values 0.001).



Prevalence of high risk HPV types and presence of multiple types by cytology outcomes

Conclusions: In the largest study of cervical HPV genotypes in HIV-infected women in the Americas, infection by high risk HPV types other than 16 or 18 and infection by more than one high risk type were common. Infection by more than one high risk type and CD4+ lymphocyte count were more strongly associated with abnormal cervical cytology than any individual high risk HPV type, highlighting the need for multi-valent HPV vaccine strategies.

857 Comparison of Three Female Genital Tract Sampling Techniques for HIV RNA Recovery

Catherine S. Todd[1]; Shameem Jaumdally[2]; Heidi E. Jones[3]; Hoyam Gamieldien[2]; Nontokozo Langwenya[4]; Landon Myer[4]; Donald R. Hoover[5]; Jo-Ann Passmore[1]

[1]FHI360, Bangkok, Thailand; [2]University of Cape Town, Cape Town, South Africa; [3]Hunter College, CUNY School of Public Health, New York, NY, US; [4]University of Cape Town, Cape Town, South Africa; [5]Rutgers New Jersey Medical School, Piscataway, NJ, US

Background: Although measuring HIV RNA shedding in women is an important element of HIV prevention research, there is no consensus on optimal female genital tract sampling methods for HIV RNA recovery, including the menstrual cup (MC). We hypothesized that MC specimens provide greater genital tract HIV RNA recovery than endocervical swab (ECS) or swab-enriched cervicovaginal lavage (eCVL).

Methods: This study, nested within a clinical trial assessing intrauterine device safety and acceptability for HIV-infected women with CD4>350 cells/mm^3, collected MC, ECS, and eCVL genital tract samples from consenting women during enrollment (sampling order MC/ECS/eCVL), 3-month (ECS/eCVL/MC), and 6-month (eCVL/MC/ECS) follow-up visits. At all visits, women self-inserted the MC for $\geq$45 minutes prior to clinician removal. ECS was collected with flocked swabs; eCVL combined an additional ECS with 5 mL saline lavage. At processing, MC secretions were weighed then diluted at 1 gm/10-fold mL phosphate-buffered saline. Matched aliquot (1 mL) sets of MC, ECS, and eCVL samples from each woman/visit were tested for HIV RNA concentration with PCR. Paired comparisons between methods were analyzed using McNemar's exact tests for dichotomous outcomes and sign-rank test for medians of continuous measures.

Results: In 39 participants, (39 enrollment, 20 3-month, and 6 6-month samples) women had a median age of 30 years (IQR 26-33). Median baseline plasma VL was 3.91 $\log_{10}$ copies/mL (range: non-detectable - 5.35 $\log_{10}$ copies/mL). Median MC sample weight was 0.34 gm (range: 0.02-1.52 gm). MC samples with detectable HIV RNA had greater volume (0.37 gm (IQR: 0.29, 0.61), n=40 vs. 0.26 gm (IQR: 0.19, 0.38), n=23; unadjusted Mann Whitney, p=0.02), but did not differ by median insertion time (both groups=95 minutes). MC samples were significantly more likely to have detectable HIV RNA than ECS and eCVL at enrollment (63% vs. 43% and 44%, respectively) and higher median HIV RNA levels than ECS or eCVL at both enrollment and 3 month follow-up (Table). In pooled analysis of women with quantifiable HIV RNA, the unadjusted median difference between MC and eCVL VL was 0.6 (IQR 0.3, 0.8, p<0.001) $\log_{10}$ copies/mL, 0.8 (IQR 0.3, 1.2, p<0.001) between MC and ECS, and -0.2 (IQR -0.8, 0.3, p=0.31) between ECS and eCVL.

Table. Comparison of detection and quantity of female genital HIV RNA viral load between specimen collection methods (n=39).

Enrollment Visit (n=39)	Menstrual Cup (MC), n=38	Endocervical Swab (ECS), n=37	Endocervical Lavage (eCVL), n=39	p, MC vs. ECS	p, MC vs. eCVL	p, ECS vs. eCVL
Detectable genital VL (n, %)	24, 63.2	16, 43.2	17, 43.6	0.02	0.01	1.00
Median VL (IQR)*	3.0 (1.3, 3.6)	1.3 (1.3, 2.8)	1.6 (1.3, 2.9)	<0.001	<0.001	0.49
Month 3 Visit (n=20)	MC, n=19	ECS, n=20	eCVL, n=20			
Detectable Genital VL (n, %)	13, 68.4	9, 45.0	12, 60.0	0.12	1.00	0.25
Median VL (IQR)*	3.2 (1.3, 3.7)	2.3 (1.3, 2.8)	2.4 (1.3, 3.1)	0.002	0.003	0.046

IQR=interquartile range

VL= HIV RNA viral load

* ND = non-detectable assigned value of 20 copies/mL, NQ=non-quantifiable assigned value of 40 copies/mL, all values reported as $\log_{10}$ copies/mL.

** Matched Mc-Nemar Exact for 2x2 proportions, Wilcoxon matched-pairs signed-rank for median differences

Conclusions: MC sampling is a more sensitive collection method for HIV RNA, yielding greater quantities, generally >0.5 $\log_{10}$ copies/mL, than the eCVL and ECS and offers a method with a known dilution factor for enhanced precision.

THURSDAY, FEBRUARY 26, 2015

Session P-S3 Poster Session

Poster Hall

2:30 pm – 4:00 pm

Hormonal Contraception

858 CCR5 Expression in HIV-Uninfected Women Receiving Hormonal Contraception

Athe Tsibris[1]; Gaia Sciaranghella[2]; Cuiwei Wang[3]; Kerry Murphy[4]; Zaher Mehri[5]; Ruth M. Greenblatt[6]; Mardge Cohen[7]; Elizabeth Golub[8]; Heather Watts[9]; Mary A. Young[3]

[1]Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, US; [2]Ragon Institute of MIT, MGH and Harvard, Boston, MA, US; [3]Georgetown University Medical Center, Washington, DC, US; [4]Albert Einstein College of Medicine, Bronx, NY, US; [5]University of Vermont College of Medicine, Burlington, VT, US; [6]University of California San Francisco, San Francisco, CA, US; [7]Stroger Hospital and Rush University and CORE Center, Chicago, IL, US; [8]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [9]The Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US

Background: Hormonal contraception may influence a woman's susceptibility to HIV-1 infection. HIV infectivity increases as host receptor and coreceptor expression levels increase. We investigated the effect of hormonal contraception on HIV-1 receptor and coreceptor peripheral blood mononuclear cell (PBMC) expression.

Methods: We used participant samples collected from The Women's Interagency HIV Study (WIHS) between 2004 to 2011 and determined the CD4, CCR5, and CXCR4 expression levels on PBMC from HIV-uninfected women who used depot medroxyprogesterone acetate (DMPA, n=32), the levonorgestrel releasing intrauterine device (LNG-IUD, n=27), or oral contraceptive pills (OCP, n=32). Women who did not use hormonal contraception (n=33) served as a comparator group. Groups were matched by age and race and one sample per participant per group was analyzed. Our monoclonal antibody panels identified monocyte, monocytoid dendritic cell, plasmacytoid dendritic cell, $CD8^+$ T cell, and $CD4^+$ T cell subpopulations. Monocytoid and plasmacytoid dendritic cells were analyzed together as a combined dendritic cell (DC) group. We compared the proportions of cells expressing CD4 and HIV coreceptors.

Results: LNG-IUD users had an increased proportion of $CD4^+$ and $CD8^+$ T cells that expressed CCR5 (4.8 ± 0.4% and 12.5 ± 1.2%, respectively), relative to women on OCP (3.1 ± 0.3% and 8.2 ± 0.7%, $p<0.01$ and $p<0.05$) or no hormonal contraception (3.4 ± 0.3% and 7.6 ± 0.6%, $p<0.05$ and $p<0.01$). LNG-IUD use was associated with a 35% relative increase in the proportion of helper T cells that expressed CCR5 over that observed with the use of OCP and a 29% increase when compared to the use of no hormonal contraception. Increased CCR5 expression was associated with changes on central (T_{CM}) and effector memory (T_{EM}) T cells ($p<0.01$ for all comparisons). Relative increases of 6-12% in the magnitude of cellular T_{CM} and T_{EM} CCR5 expression were observed in the DMPA and LNG-IUD groups, compared to the OCP and no hormonal contraception groups ($p<0.01$ for all comparisons). No differences in the proportion of monocytes or dendritic cells that expressed CCR5, or hormone-associated changes in PBMC CD4 or CXCR4 expression levels, were detected.

Conclusions: The use of the LNG-IUD and, to a lesser extent, DMPA was associated with increased CCR5 expression on peripheral T cells. Comparative work in female reproductive tract tissues and blood is needed to further evaluate contraception-associated increases in CCR5 expression.

859 Estrogen Replacement in Healthy Postmenopausal Women Reduces %CCR5+ CD4+ T Cells

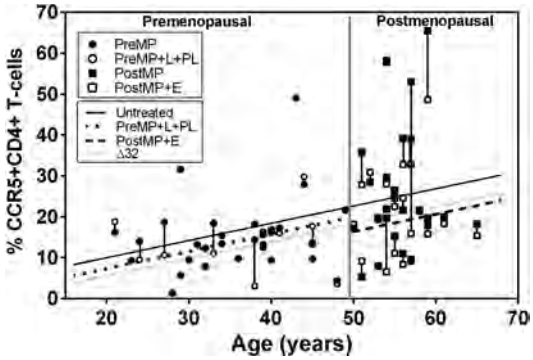
Amie Meditz[1]; Samantha MaWhinney[2]; Kerrie Moreau[2]; Kelsey Melander[2]; Joy Folkvord[2]; Wendy Kohrt[2]; Margaret Wierman[2]; Elizabeth Connick[2]

[1]Boulder Community Health, Boulder, CO, US; [2]University of Colorado Anschutz Medical Campus, Aurora, CO, US

Background: CCR5 is elevated on whole blood and cervical CD4+ T cells of healthy postmenopausal women (postMP) compared to premenopausal women (preMP), suggesting increased risk of HIV acquisition in older women. To test whether estrogen (E) downregulates CCR5, we evaluated CCR5 expression in healthy postMP who received E replacement and preMP who underwent medical induction of menopause.

Methods: Healthy HIV- women were recruited to A) 2 studies of E patch (estradiol 0.05 or 0.075 mg/day) versus placebo (PL) in postMP; B) a study of preMP who underwent menopause induction via GnRH agonist Lupron (L) with add-back E patch (0.075 mg/day) or placebo (PL); and C) an observational study of preMP. Blood was collected from preMP (early follicular phase) and postMP at baseline. Repeat sampling occurred 2 days to 4 weeks following E or PL in postMP and 4 weeks following dosing of L+E or L+PL to preMP. %CCR5+ and %CCR5+HLA-DR+CD38+ (activated) CD3+CD4+ cells were determined by flow cytometry, and CCR5Δ32 genotype by molecular analyses. Data were analyzed using mixed models and nonparametric methods.

Results: In postMP after E, %CCR5+ and %CCR5+activated cells tended to decrease (median Δ, -3.4%; p=0.16, and -5.8%; p=0.28, respectively; n=10). PostMP+PL exhibited small changes in these parameters (median Δ, -0.4%, p=0.10 and -0.8%; p=0.60, respectively; n=15). In preMP, there were statistically nonsignificant decreases after L+PL in %CCR5+ (median Δ, -0.88%, p=0.28; n=11) and %CCR5+activated cells (median Δ, -3.4%, p=0.57; n=9). PreMP who received L+E had median changes of -0.23% (p=0.82; n=9) and 7.4% (p=0.69; n=7), respectively. Across all subjects, after controlling for CCR5Δ32 genotype (p=0.29), there was a 4.2% increase in %CCR5+ (95% CI 1.5%, 6.9%; p=0.003) for every 10-year age increase (Figure). PostMP+E had 6.2% lower %CCR5+ than postMP (95% CI -10.9%, -1.6%; p=0.01). Estimated %CCR5+ tended to be lower in PreMP following L+PL (-2.7%, 95% CI -7.1%, 1.8%; p=0.23), inconsistent with the hypothesis that induction of menopause would substantially increase CCR5 expression. Similar trends were seen in %CCR5+activated cells.



Conclusions: E replacement reduces %CCR5+CD4+ T cells in healthy postMP, suggesting it could decrease HIV acquisition in this group. Lack of a sizeable increase in %CCR5+ in healthy preMP after medically induced menopause may be due to short duration of ovarian hormone suppression, unknown effects of Lupron, or different age-related effects of E on CCR5 expression.

860 Progesterone Increases Are Associated With HIV Susceptibility Factors in Women

Alison Y. Swaims[1]; Tammy Evans-Strickfaden[1]; L Davis Lupo[1]; Alfredo Aguirre[2]; Anandi Sheth[2]; Igho Ofotokun[2]; Clyde E. Hart[1]; **Richard E. Haaland**[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]Emory University School of Medicine, Atlanta, GA, US

Background: Native progesterone and progestin-based hormonal contraception are suspected of increasing women's risk for acquiring sexually transmitted HIV. How progesterone and progestin-based contraceptives affect HIV target cells in women is uncertain. We investigated whether a population of HIV target cells in women, CD4 T lymphocytes, changes cell surface expression of the HIV CCR5 coreceptor, cell activation markers and response stimulation throughout a normal menstrual cycle.

Methods: Peripheral blood mononuclear cells (PBMCs) isolated from 7 women at 5 time points throughout their normal menstrual cycles were tested for expression of the HIV coreceptor CCR5 and the activation marker CD38 using flow cytometry. PBMCs were also stimulated *ex vivo* in the presence of Golgi transport inhibitors and intracellular production of IL-2, IFN-g and TNF-a was detected using flow cytometry. Plasma estradiol and progesterone were measured at each time point using a luminex multiplex assay. A sustained rise in plasma progesterone levels marked the beginning of the luteal phase of the menstrual cycle.

Results: The proportion of CCR5 and CD38 expressing CD4 memory T cells increased from 4% to 7% (p=0.03) from the follicular to luteal phase in 6 of 7 women. The proportion of *ex vivo* stimulated CD4 T cells with detectable intracellular TNF-a increased from 31% to 52% (p=0.006) from the follicular to the luteal phase while production of intracellular IL-2 and IFN-g remained unchanged. Increased populations of TNF-a producing cells were associated with higher plasma progesterone levels (p=0.04). The increase in TNF-a production occurred almost exclusively in cells which were also expressing IL-2 or both IL-2 and IFN-g. Time points with detectable increases in TNF-a production were the same or immediately preceding those where CCR5 and CD38 expression increased in 6 of 7 women. Estradiol levels were not associated with changes in CCR5, CD38, or *ex vivo* cytokine production.

Conclusions: Our results suggest that increases in endogenous progesterone during the luteal phase of the menstrual cycle are associated with HIV target cells that have increased expression of the HIV coreceptor CCR5, higher activation levels, and an increased response to stimulation. Knowing if these progesterone effects exist in the genital mucosa of women could be an important measure for identifying risk factors of progestin-based hormonal contraceptives.

861 Changes in Vaginal Microbiota and Cytokines in HIV-1-Seronegative Women Initiating DMPA

Alison C. Roxby[1]; David N. Fredricks[2]; Katherine Odem-Davis[1]; Kristjana H. Ásbjörnsdóttir[1]; Linnet Masese[1]; Tina L. Fiedler[2]; Walter Jaoko[3]; James N. Kiarie[3]; Julie M. Overbaugh[2]; R Scott McClelland[1]

[1]University of Washington, Seattle, WA, US; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [3]University of Nairobi, Nairobi, Kenya

Background: Depot-medroxyprogesterone acetate (DMPA) has been associated with HIV acquisition in African women. We studied changes in vaginal microbiota and inflammatory milieu after DMPA initiation, a mechanism through which DMPA may modify HIV susceptibility.

Methods: In a prospective cohort study of high-risk Kenyan women, we collected monthly vaginal swabs over 1 year pre- and post-DMPA to evaluate microbiota and immune mediators. All women initiating DMPA were included. Using quantitative PCR with specific bacterial primers, we measured quantities of *Lactobacillus crispatus, L. jensenii, L. iners*, *Gardnerella vaginalis*, and total bacterial load (16S rRNA gene levels) on vaginal swabs. Six vaginal immune mediators were measured with ELISA. Trends in detection and quantity of bacteria were estimated by logistic and linear mixed-effects regression models; cytokine trends associated with DMPA use were estimated using tobit random-effects regression.

Results: From 2010-2012, 15 HIV-seronegative women initiated DMPA, contributing 85 visits (median 6 visits/woman (range 3-8)). The median time of DMPA-exposed follow-up was 8.4 months (range 1.5-11.6). Seven women (46%) had bacterial vaginosis (BV) within 70 days before DMPA start. *L. iners* was detected in 13 women (87%) prior to DMPA start, but other lactobacilli were rarely detected. *G. vaginalis,* present in all women pre-DMPA, declined by 0.21 $\log_{10}$ copies/swab per month after DMPA exposure (p=0.011). Total vaginal bacterial load declined by 0.08 $\log_{10}$ copies/swab per month of DMPA use (p=0.017). Sustained declines in quantities of interleukin (IL)-6 (p=0.025), IL-8 (p=0.041) and IL-1 receptor antagonist (p<0.001) were noted after starting DMPA. Nine women (60%) had *L. crispatus* detected after DMPA start; *L. crispatus* detection was significantly correlated with lower levels of IL-6 and IL-8 (p=0.009, p=0.02 respectively). No decrease in BV, vaginal pH or discharge was seen after DMPA start. Declines in *G. vaginalis* and immune mediators were preserved after adjustment for sexual behavior, condom use, BV, antibiotic use and vaginal washing.

Conclusions: Initiation of DMPA led to sustained shifts in vaginal bacterial concentrations and levels of inflammatory mediators. We adjusted for likely behavioral and biological confounders, providing greater evidence that changes seen may be strongly related to DMPA. Further studies are warranted to outline specific components of the vaginal microbiota influenced by DMPA use, and the impact on HIV susceptibility.

862 A Thinned Vaginal Stratum Corneum Is a Susceptibility Factor for SHIV Acquisition

Ellen Kersh; Jana Ritter; Katherine Butler; Sharon Dietz Ostergaard; Debra Hanson; Sherif Zaki; Janet McNicholl

US Centers for Disease Control and Prevention, Atlanta, GA, US

Background: Biological mechanisms for increased HIV acquisition risk due to hormonal influences in women remain insufficiently understood. Vaginal epithelial thinning occurs during periods of high progesterone such as hormonal contraception or the luteal menstrual phase. It is unclear whether and to what extent this facilitates HIV entry. The study objective was to quantitatively evaluate vaginal epithelial thinning during the menstrual cycle and to determine any correlative relationship with susceptibility to SHIV infection.

Methods: We previously estimated vaginal SHIVSF162P3 acquisition time points after repeated virus exposure throughout the menstrual cycles of 43 pigtail macaques (Macaca nemestrina). Cycles of 16 different macaques were monitored for 80 days to determine days 1-16 and 17 and up (follicular and luteal phases, respectively). Vaginal biopsies were collected in the two phases. The superficial, non-nucleated (Stratum corneum) and underlying nucleated cell layers were quantitated by microscopy supported by image analysis software.

Results: The vaginal epithelium was thicker in the follicular than the luteal phase (mean 350, 230 micrometers [um] respectively; p=0.006, Mann-Whitney test). To get a more dynamic picture of thinning, we analyzed four-day segments of the cycle and found the epithelium was thickest on days 13-16 (mean 389 um), and thinnest on days 29-32 (134 um). A large relative thickness change occurred in the S. corneum with a mean 106 and 16 um at these times, respectively. The number of animals with estimated SHIV acquisition in each four-day menstrual cycle segment strongly correlated with thinness of the S. corneum (Pearson's r = 0.7, p<0.05), but only moderated correlated with the nucleated cell layer (Pearson's r=0.5, p=0.17).

Conclusions: These data provide a more detailed, dynamic picture of the layered vaginal epithelium during progesterone changes than previously described. Extensive relative thinning occurred in the superficial S. corneum. This glycogen-rich layer has terminally differentiated cells, likely maintains the vaginal microbiome and exfoliates invading pathogens. Although the relationship with infection data could only be studied using aggregate data from animals in a separate study, the data support S. corneum thinning as a factor in susceptibility to SHIV infection. A better understanding of innate resistance mechanisms to vaginal SHIV or HIV infection could lead to novel HIV prevention strategies for women.

TUESDAY, FEBRUARY 24, 2015

Session P-T1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

How Fast? How Often? Achieving Viral Suppression in Pregnant and Postpartum Women

863 Specific Effects of ZDV, 3TC and LPV/r on HIV-1 RNA Viral Load During Pregnancy

Patumrat Sripan[1]; Sophie Le Coeur[5]; Lily Ingsrisawang[2]; Tim R. Cressey[3]; Jean-Marc Tréluyer[6]; Naïm Bouazza[4]; Frantz Foissac[4]; Gonzague Jourdain[3]; Marc G. Lallemant[3]; Saïk Urien[7]

[1]ED420, University of Paris Sud 11, Paris Descartes, Paris, France/PHPT-IRD UMI 174, Chiang Mai, Thailand/Department of Statistics, Faculty of Science, Kasetsart University, Bangkok, Thailand; [2]Department of Statistics, Faculty of Science, Kasetsart University, Bangkok, Thailand; [3]PHPT-IRD UMI 174, Faculty of Associated Medical Sciences, Chiang Mai University/Harvard School of Public Health, Chiang Mai, Thailand; [4]EA 08 Université Paris Descartes, Sorbonne Paris Cité, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, Paris, France; [5]Institut d'Etudes Démographiques, Institut de Recherche Pour le Développement (UMR 196 CEPED), Paris, France/Harvard School of Public Health, Boston, MA, USA/Faculty of Associated Medical Science, Chiang Mai University, Chiang Mai, Thailand; [6]EA 08 Université Paris Descartes, Sorbonne Paris Cité, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, Service de Pharmacologie Clinique, AP-HP, Groupe Hospitalier Paris Centre, CIC-0901 Inserm, Cochin-Necker, Paris, France; [7]EA 08 Université Paris Descartes, Sorbonne Paris Cité, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, CIC-0901 Inserm, Cochin-Necker, Paris, France

Background: HIV-infected women commonly receive zidovudine (ZDV) + lamivudine (3TC) + lopinavir/ritonavir (LPV/r) during pregnancy for the prevention of mother-to-child transmission (PMTCT) in Thailand. Our aims were to evaluate the role of 3TC added to ZDV+LPV/r and the specific effect of each drug on maternal HIV-1RNA viral load (VL) reduction for the PMTCT.

Methods: A total of 1,655 plasma VL levels from 702 pregnant women enrolled in the PHPT-5 perinatal HIV prevention trial in Thailand (NCT01511237, NCT00409591) were included. ART naïve pregnant women received either (1) ZDV only (plus nevirapine at onset of labor); (2) ZDV+LPV/r; or (3) ZDV+3TC+LPV/r. HIV-1 RNA VL time courses were analysed using non-linear mixed effect modelling and dependent on VL at treatment initiation and duration of treatments. An Emax response model was used to describe the impact of these ARV regimens on VL reduction during pregnancy. A mechanistically-based equation was developed to determine the contribution of each drug assuming ZDV and 3TC have the same target and mechanism of action, and the effect of LPV/r was added as a separate component.

Results: Of the 702 women, 278 (40%) received ZDV monotherapy, 146 (20%) ZDV+LPV/r and 278 (40%) ZDV+3TC+LPV/r during pregnancy. The maximum effect of each regimen on HIV-1 RNA VL was significantly different (p<0.02), with 1.67, 3.8 and 4.57 $\log_{10}$copies/mL reduction for ZDV alone, ZDV+LPV/r and ZDV+3TC+LPV/r, respectively. Time to reach half of maximum effect (T_{50}) was significantly longer with ZDV alone compared with ZDV+3TC+LPV/r (p<0.001). However there was no significant difference between ZDV+LPV/r and ZDV+3TC+LPV/r (p=0.13). The mechanistically-based model estimated that 110 days of ZDV or 3TC were necessary to achieve half of ZDV or 3TC maximum effect on viral load suppression (maximum effect: minus 1.38 and 2.05 $\log_{10}$copies/mL, respectively) whereas only 10 days of LPV/r were necessary to achieve half of LPV/r maximum effect (maximum effect: minus 2.32 $\log_{10}$ copies/mL). Using the mean VL at treatment initiation (4.07 $\log_{10}$ copies/mL), the model indicated that the addition of 3TC reduced the time to undetectable VL (<50copies/mL) by 3 weeks: 7.3 weeks with ZDV+LPV/r compared with 4.4 weeks for ZDV+3TC+LPV/r assuming a common T_{50} for ZDV and 3TC.

Conclusions: The addition of 3TC to ZDV+LPV/r during pregnancy reduces time to reach undetectable VL in pregnant women, especially those with a high VL at treatment initiation and subsequent high risk of MTCT.

864 Viral Suppression After Antiretroviral Therapy Initiation in Pregnancy in South Africa

Landon Myer[1]; Tamsin Phillips[1]; Nei-Yuan Hsiao[2]; Allison Zerbe[3]; Jo Ramjith[1]; Linda-Gail Bekker[1]; James A. McIntyre[4]; Elaine J. Abrams[3]

[1]University of Cape Town, Cape Town, South Africa; [2]National Health Laboratory Services/University of Cape Town, Cape Town, South Africa; [3]ICAP at Columbia University, New York, NY, US; [4]Anova Health Institute, Johannesburg, South Africa

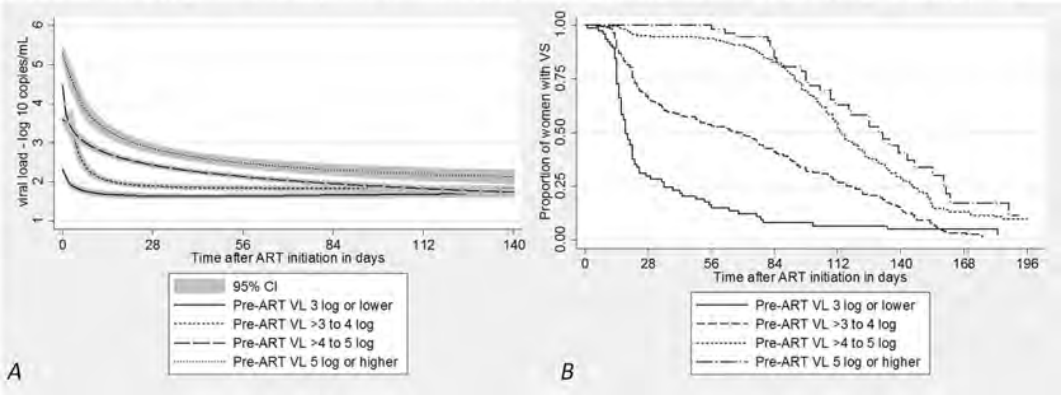
Background: HIV viral load (VL) is the principle determinant of mother-to-child transmission (MTCT) risk and rapid lowering of VL is a primary goal of antiretroviral therapy (ART) for prevention of MTCT. However there are few data on the trajectory of viral load (VL) and time to viral suppression <50 copies/mL (VS) following ART initiation in HIV-infected pregnant women.

Methods: Consecutive pregnant women initiating ART in Cape Town, South Africa were recruited into a prospective cohort from ART initiation through delivery, with VL measured immediately prior to initiation (pre-ART), 1-4 weeks after initiation, during the 3rd trimester, and at 1 week postpartum. All women initiated TDF+FTC+EFV. Analyses examined changes in log VL trajectories after initiation using non-linear mixed models, the proportions of women achieving VS over time using product-limit methods, and the probability of VS at delivery using logistic regression.

Results: From April 2013 to May 2014, 629 ART-naïve pregnant women were enrolled (median age, 28 years; median CD4 cell count, 343 cells/μL; median gestation age (GA), 21 weeks; median VL, 4.0 log10 copies/mL [IQR: 3.4-4.6]). Most women achieved VL<3 log within 4 weeks of ART start (Figure 1a) but the median time to VS<50 copies/mL was 14.1 weeks (95% CI, 13.3-15.3). Time to VS was strongly influenced by pre-ART VL: women with VL <3, 3-4, 4-5 and >5 log10 copies/mL before ART initiation had median times to VS of 2.9, 9.6, 17 and 18.9 weeks, respectively (p<0.001; Figure 1b). 75% of women achieved VS by delivery. Adjusting for age and past ARV exposure, decreased probability of VS at

delivery was associated with higher pre-ART VL (relative odds [RO] 0.39 for a 1-log increase in pre-ART VL, p<0.001); later GA at ART initiation (RO, 0.87 for a 1-week increase in GA at ART initiation, p<0.001); and inversely associated with higher pre-ART CD4 cell counts (RO, 1.08 for a 50-unit increase in pre-ART CD4 cell count, p=0.025).

Figure 1. Viral load declines following ART initiation in pregnancy: (a) fractional polynomial modelling of VL declines over time and (b) time to viral suppression <50 copies/mL, by pre-ART VL categories



Conclusions: These data provide novel evidence on VS after ART initiation in pregnancy in African populations using a standardised first-line regimen. The rapid early declines in VL to <3 log within a month on ART in most women are encouraging. However one-quarter of the cohort still had detectable VL at the time of delivery, demonstrating the importance of early initiation of ART in pregnancy.

865 Maternal Viral Load in the Context of PMTCT B+ Within the Kabeho Study in Kigali

Emily A. Bobrow[1]; Placidie Mugwaneza[2]; Gilles F. Ndayisaba[3]; Dieudonne Ndatimana[3]; **Michelle Gill**[1]; Heather J. Hoffman[4]; Cyprien Baribwira[5]; Laura Guay[1]; Anita Asiimwe[6]
Kabeho Study Team

[1]Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC, US; [2]Ministry of Health, Kigali, Rwanda; [3]Elizabeth Glaser Pediatric AIDS Foundation, Kigali, Rwanda; [4]George Washington University Milken Institute School of Public Health, Washington, DC, US; [5]University of Maryland, School of Medicine, Kigali, Rwanda; [6]Rwanda University Teaching Hospitals, Kigali, Rwanda

Background: In April 2012, Rwanda started to implement a policy to initiate HIV-positive pregnant women on lifelong antiretroviral treatment (ART) ('Option B+'). In April 2013, EGPAF and the Ministry of Health began the Kigali Antiretroviral and Breastfeeding Assessment for the Elimination of HIV (Kabeho) Study. The study will determine 18 and 24 month HIV-free survival of a cohort of HIV-exposed children in the PMTCT program.

Methods: From April 2013-January 2014, 608 HIV-positive women on triple drug ART in the third trimester of pregnancy or within two weeks post-delivery were enrolled in the observational prospective cohort from 14 health facilities in Kigali. After providing written informed consent, women underwent enrollment, including HIV and ART-related history and adherence, and a blood draw for viral load (VL) testing by RNA-PCR (Roche).

Results: The median time women knew their HIV-positive status was 38.0 months (IQR 4.7–83.5). The most common ARV regimen (56.6%, 344/608) was TDF/3TC/EFV. Overall, 35.2% (n=214) of women reported taking another regimen previously; 21.5% (n=130) due to PMTCT during an earlier pregnancy. At enrollment, women were on ART for a median of 13.4 months (IQR 2.96–48.8); median time on current ART was 9.2 months (IQR 2.3-34.8). The adherence rate based on a 3-day ART recall was 90.9%. Side effects were reported in the past month by 17.5% (n=105) of women, with dizziness as most common (n=53).

Half of women (52.2%, 316/606) had undetectable VL. Figure 1 shows the distribution of VL by ART duration. Logistic regression using GEE (N=579) indicates women were more likely to have a detectable VL if they had no education (AOR=2.21, 95% CI: 1.31, 3.73), reported side effects in the past month (AOR=1.96, 95% CI: 1.37, 2.81), and had been on ART less than four months, when compared to those with ART exposure from 4-12 months (AOR=3.98, 95% CI: 2.11, 7.50), 12-24 months (AOR=6.04, 95% CI: 2.47, 14.76), and 24-36 months (AOR=5.57, 95% CI: 2.38, 13.05). VL slightly decreased beyond 36 months on ART (AOR=3.56, 95% CI: 1.69, 7.50).

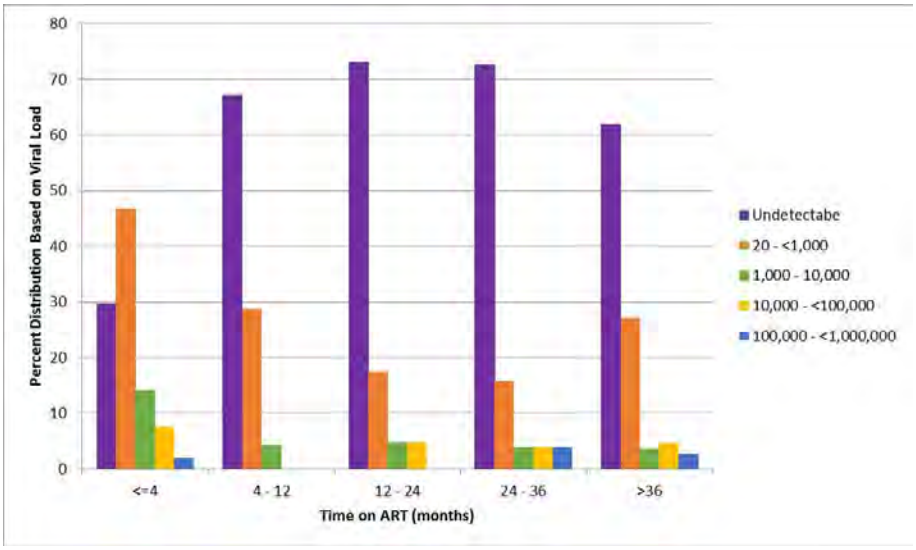


Figure 1. Distribution of viral loads stratified by time on ART.

Conclusions: High rates of ART adherence in the antenatal/peripartum period under Option B+ were reported. However, only half of women had undetectable VL at enrollment. Findings suggest longer ART duration may be needed for women in PMTCT to achieve viral suppression. Testing for ARV resistance is planned. Analysis of the cohort will incorporate specific regimen information, regimen changes, longitudinal VL, and adherence over time.

866 ART Response Among Pregnant and Postpartum Women With Acute Versus Chronic HIV-1

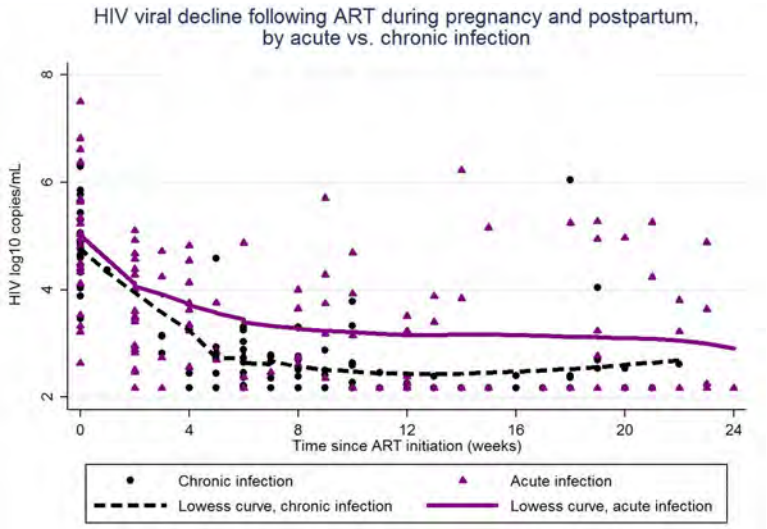
Alison L. Drake[1]; John Kinuthia[2]; Daniel Matemo[2]; Barbra Richardson[1]; Michael Chung[1]; James N. Kiarie[2]; Sandy Emery[3]; Julie M. Overbaugh[3]; Grace John-Stewart[1]

[1]University of Washington, Seattle, WA, US; [2]University of Nairobi, Nairobi, Kenya; [3]Fred Hutchinson Cancer Research Center, Seattle, WA, US

Background: Risk of mother-to-child HIV-1 transmission (MTCT) is high among women with acute HIV-1 infection (AHI). Plasma HIV-1 viral load (PVL) can be substantially reduced with antiretroviral therapy (ART), which reduces MTCT risk; however, viral decline post-ART among pregnant and postpartum women with AHI has not been well characterized. We compared virologic and immunologic responses to ART between pregnant and postpartum women with AHI versus chronic HIV-1 infection (CHI) in Kenya.

Methods: Women with AHI (detected by nucleic acid amplification tests conducted serially during pregnancy and postpartum) initiating ART (3TC, EFV, and either ZDV or TDF) were identified in a prospective study in Western Kenya. Women with CHI who initiated ART (AZT, 3TC, and NVP) during pregnancy in a prior clinical trial in Nairobi and had available PVL and CD4 data were selected for comparison. Blood was collected serially in both studies to compare post-ART changes in PVL and CD4; PVL was evaluated using the same laboratory and assay for both studies. Linear mixed effects models were used to model rate of PVL decline and demographics and CD4 were compared by the Wilcoxon Rank-Sum Test.

Results: Data from 25 women with AHI and 30 women with CHI were compared. Women with AHI were younger (median 21 vs. 30 years; p=.006) and less likely to be married (97% vs. 76%; p=.02) than women with CHI. Mean baseline PVL was similar (AHI: 4.52, CHI: 4.37 log_{10}copies/mL; p=.5). Baseline CD4 count was significantly higher in women with AHI than CHI (median 542 vs. 267, respectively; p<.001). Average monthly decline in PVL during 10 weeks post-ART was greater among women with CHI (-1.04 log_{10} copies/mL; 95% Confidence Interval [CI]:-1.50,-0.57) than AHI (-.67 log_{10}copies/mL, 95% CI:-0.84, -0.47); CHI versus AHI PVL decline p=.007), adjusting for baseline CD4. Viral decline was less pronounced 10 to 24 weeks post-ART in both groups, but remained steeper among women with CHI versus AHI (-.15 versus -.03 log_{10}copies/mL, respectively; p=.002). Change in CD4 counts 6 months post-ART was similar (p=.5).



Conclusions: Rate of viral decline following ART was significantly slower among women with AHI than CHI, perhaps because HIV-specific immune responses that work synergistically with ART to decrease PVL have not yet developed in AHI. Strategies to accelerate viral decline, such as ART-intensification among AHI during pregnancy and postpartum, may be useful to reduce MTCT risk.

TUESDAY, FEBRUARY 24, 2015

Session P-T2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Rates and Risks of MTCT and HIV-Free Survival

867 No Perinatal Transmission of HIV-1 in Women Efficiently Treated Since Conception

Laurent Mandelbrot[1]; Roland Tubiana[2]; Jérome Le Chenadec[3]; Catherine Dollfus[4]; Albert Faye[5]; Christine Rouzioux[6]; Anais Perilhou[3]; **Josiane Warszawski**[7]; Stéphane Blanche[6]
The ANRS-EPF (CO1/CO10/CO11) Study Group

[1]AP-HP, Hôpital Louis Mourier - INSERM U1018, CESP - Université Paris 7, Colombes, France; [2]AP-HP, Hôpital Pitié Salpêtrière - INSERM, U943, Paris, France; [3]INSERM CESP U1018, Le Kremlin-Bicetre, France; [4]AP-HP, Hôpital Trousseau, Paris, France; [5]AP-HP, Hôpital Robert Debre-University Paris 7, Paris, France; [6]AP-HP, Hôpital Necker-Enfants Malades, University Paris-Descartes, Paris, France; [7]University Paris-Sud - INSERM CESP U1018 - AP-HP Hopital Bicetre, Le Kremlin-Bicetre, France

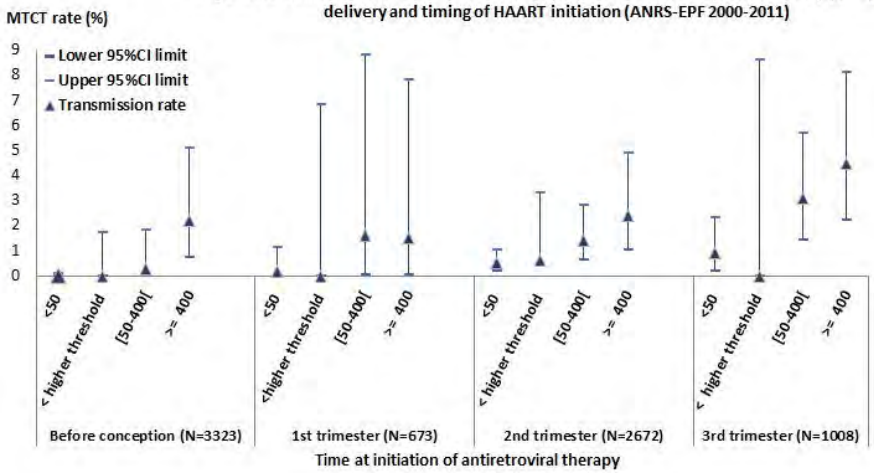
Background: The efficacy of prevention of perinatal transmission of HIV-1 is dependent on both viral load and treatment duration. The objective of this study was to determine whether initiating highly active antiretroviral treatment (HAART) before conception has the potential to eliminate perinatal transmission.

Methods: In the national prospective multicentre French Perinatal Cohort (EPF), perinatal transmission (PT) was analysed according to the viral load (VL) in maternal plasma near delivery and timing of HAART initiation in 7937 HIV-infected women from 2000 to 2011.

Results: The overall incidence of PT was 56/7937 (0.7%). No case of transmission occurred among the 2588 women who were on HAART before conception, without treatment interruption during the first trimester, and who delivered with a plasma VL <50 copies /mL (upper 95% confidence interval limit: 0.1%).

VL and timing of HAART initiation were independently associated with PT in logistic regression (Fig 1). Regardless of viral load, the transmission rate increased from 0.2% for women initiating HAART prior to conception to 0.4% during the 1st trimester, 0.9% during the 2nd trimester and 2.2% during the 3rd trimester; p<0.001. Regardless of timing of HAART initiation, the rate was higher for women with VL between 50 and 400 copies/mL near delivery than for those with < 50 copies/mL: adjusted odds ratio = 3.5 [95%CI: 1.7 -7.3].

Fig 1: Rate of mother-to-child transmission (MTCT) of HIV, according to viral load (cp/mL) near delivery and timing of HAART initiation (ANRS-EPF 2000-2011)



Conclusions: Perinatal HIV-1 transmission is virtually zero in mothers who start antiretroviral therapy before conception and maintain suppression of the plasma viral load.

868 Predictors of Perinatal HIV Transmission in the BAN Study

Sascha R. Ellington[1]; **Athena P. Kourtis**[1]; Ali Fokar[2]; Charles S. Chasela[4]; Dumbani Kayira[3]; Gerald Tegha[3]; Denise J. Jamieson[1]; Charles M. van der Horst[2]
The BAN Study Team

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]University of North Carolina Project Lilongwe, Lilongwe, Malawi; [4]University of Witwatersrand, Johannesburg, South Africa

Background: Mother-to-child transmission of HIV (MTCT) can occur in utero, at the time of delivery, or postnatally through breastfeeding. In breastfeeding populations and in the absence of antiretroviral (ARV) prophylaxis, up to 70% of MTCT occurs in utero or intrapartum.

Methods: We conducted a case cohort study to assess predictors of perinatal (in utero or intrapartum) MTCT using data from the Breastfeeding, Antiretrovirals and Nutrition (BAN) study. All mothers in labor and their infants received single-dose nevirapine and zidovudine/lamivudine for 7 days. The BAN study randomized ARV-naïve women with CD4 count>200/250 to maternal ARV, infant nevirapine or control to examine the role of ARV on postnatal MTCT. Cases were 119 mothers that transmitted HIV to their infants by 2 weeks postpartum; controls were mothers whose infants were uninfected by 4 weeks of age (N=2120). Laboratory, clinical and demographic maternal characteristics were evaluated as predictors of perinatal MTCT in bivariate analyses and, for those variables significant in bivariate analyses when stratified or adjusted by HIV viral load (p<0.1), multivariable logistic regression.

Results: Among 119 perinatally infected infants, 115 were positive at birth and 4 were negative at birth but positive by 2 weeks of life. Transmitting mothers had significantly higher median HIV viral load during pregnancy compared to non-transmitting mothers (64,263 vs 16,393 copies/ml, p<0.001). There was one perinatal transmission in a mother with viral load <1,000 copies. Anemia was a strong predictor of perinatal MTCT in mothers with a viral load ≤10,000 copies/ml (OR 5.0, 95%CI 1.1-23.9), but not among mothers with higher viral load. After adjusting for viral load and covariates, mothers currently facing a food shortage had a 60% increased odds of perinatal MTCT (p=.01), as did those with a history of herpes zoster (OR 3.3, 95%CI 1.8-5.9), and those reporting an STI in the last 12 months (88% increased odds of perinatally transmitting HIV, p=.05).

Crude and Adjusted Odds Ratios for Perinatal HIV Transmission BAN Study, Lilongwe, Malawi 2004-2010

Variable Maternal CD4	Crude Odds Ratio	95% Confidence Interval	Adjusted Odds Ratio*	95% Confidence Interval
200-350 cells/ml	1.63	(1.02, 2.59)	--	--
350.1-500 cells/ml	1.45	(0.99, 2.31)	--	--
>500 cells/ml (referent)	1.00		--	--
Viral Load>10,000 copies/ml				
with anemia**	3.87	(1.83, 8.14)	3.63	(1.72, 7.68)
without anemia**	18.78	(4.52, 77.94)	19.45	(4.68, 80.87)
Education >primary	0.63	(0.41, 0.96)	--	--
Low Albumin (<3 g/dL)	1.67	(1.09, 2.55)	--	--
Past Medical History of Tuberculosis	2.46	(1.15, 5.28)	--	--
Facing a Food Shortage	1.50	(1.04, 2.17)	1.60	(1.10, 2.34)
Anemia during pregnancy**				
with VL≤10,000 copies/ml	5.12	(1.08, 24.25)	5.04	(1.06, 23.93)
with VL>10,000 copies/ml	1.05	(0.71, 1.57)	0.94	(0.63, 1.42)
Sexually transmitted infection in last 12 months	1.70	(0.93, 3.11)	1.88	(1.01, 3.50)
Past Medical History of Herpes Zoster	3.74	(2.15, 6.51)	3.29	(1.85, 5.87)

*Adjusted for all other variables in multivariable model

**Anemia defined as hemoglobin<11 g/dL

— Not included in multivariable model

Conclusions: Identifying factors associated with MTCT independent of viral is needed to further improve PMTCT programs. Maternal anemia, food insecurity, STI in the last 12 months, and past history of herpes zoster were significantly associated with perinatal MTCT independent of viral load in this cohort of previously untreated mothers. Maximizing maternal health will be particularly important to achieve elimination of perinatal MTCT worldwide.

869 High Rate of HIV Superinfection After Delivery: Secondary Analysis of the PEPI Trial

Andrew D. Redd[1]; Sarah Wendel[1]; Andrew Longosz[1]; Jessica M. Fogel[2]; Newton Kumwenda[3]; Sufia Dadabhai[3]; Susan H. Eshleman[2]; Stephen Porcella[4]; Thomas C. Quinn[1]; Taha Taha[3]

[1]National Institute of Allergy and Infectious Diseases, Baltimore, MD, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [4]National Institute of Allergy and Infectious Diseases (NIAID), Hamilton, MT, US

Background: HIV superinfection (SI) occurs when an infected individual acquires a distinctly new HIV strain, and can occur at rates comparable to primary HIV incidence. This study examined the risk of post-partum SI in HIV-infected women from the Post-Exposure Prophylaxis of Infants (PEPI) trial in Malawi, and evaluated if SI is associated with an increased risk of postnatal mother-to-child transmission (MTCT). PEPI demonstrated that infants who received 14 weeks of extended antiretroviral prophylaxis (ARV; nevirapine or nevirapine plus zidovudine) were at lower risk of acquiring HIV through breastfeeding than infants who received a short course of ARV prophylaxis.

Methods: Samples from women who transmitted HIV to their babies via breast milk (transmitters; infants were HIV- at six weeks of age, but positive later) were screened for HIV-SI (n=91). The 91 cases were matched as a group to women who did not transmit to their babies (non-transmitters) by study arm, follow-up time and sample availability. Samples from delivery and a follow-up visit for each woman were amplified and pyrosequenced in two genomic regions (p24 and gp41). HIV SI was established if the follow-up sample contained a new, phylogentically distinct viral population that was a greater genetic distance from the original viral strain than what would be expected based on viral evolution. HIV SI and MTCT risk were examined by logistic regression, and adjusted for study arm, viral load and CD4 count at delivery, time to resumption of sex, and breastfeeding duration.

Results: Postpartum MTCT was associated with lower initial CD4 counts (p=0.001) and higher viral loads (p<0.0001) at delivery. There were eight SIs in the transmitter group (8/91) with a rate of SI of 7.5/100 person years (pys). This compares to six SIs in the non-transmitter group (6/91) for a rate of SI of 5.3/100pys (p=0.78). HIV SI was not associated with an increased risk of postnatal MTCT after adjusting for factors that influence transmission (adjusted odds ratio=2.73, 95% confidence interval=0.67-11.17; p=0.16).

Conclusions: In this study, there was a relatively high rate of HIV SI in postnatal HIV-infected women. HIV SI did not increase the risk of postnatal MTCT in this study, which may be due to the limited sample size and the extended ARV prophylaxis in a portion of the infants. Further research in different populations will be needed to determine the relationship between HIV SI and transmission.

870 Decline in Early Mother-to-Child HIV Transmission (MTCT) Risk Over Time in Botswana

Kathleen M. Powis[1]; Gbolahan Ajibola[2]; Jean Leidner[3]; Kara Bennett[4]; Florence Chilisa[2]; Keabetwe Bedi[2]; Chipo Petlo[7]; Michael D. Hughes[8]; Roger Shapiro[5]; Shahin Lockman[6]

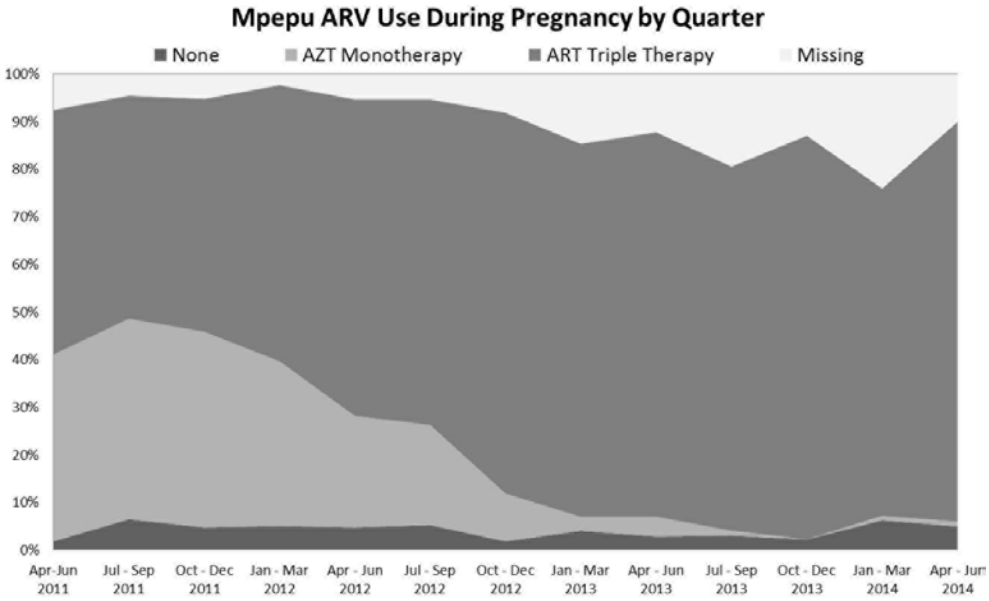
[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]Botswana Harvard AIDS Institute, Gaborone, Botswana; [3]Goodtables Data Consulting, Norman, OK, US; [4]Bennett Statistical Consulting, Inc, Ballston Lake, NY, US; [5]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US; [6]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [7]Botswana Ministry of Health, Gaborone, Botswana; [8]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US

Background: Botswana transitioned from WHO "Option A" (AZT for HIV-infected pregnant women with CD4>250 cells/mm^3) to universal triple-antiretroviral (ARV) for all pregnant women ("Option B") starting March 2011. This policy was implemented over time (and at all facilities by Jan 2013).

Methods: We used data from an ongoing trial of cotrimoxazole prophylaxis for infants born to HIV-infected women, the Mpepu study, to analyze trends in PMTCT coverage and transmission. HIV-infected women were eligible for enrollment regardless of CD4, viral load or treatment during pregnancy. ARVs were provided by Botswana Government facilities, not by the study. Mpepu infant HIV DNA PCR testing occurred at birth and 2-4 weeks of life at study sites in Gaborone, Molepolole, and Lobatse. We compared ARV regimen and MTCT rates among mother-infants pairs enrolled May 2011-Dec 2012 vs. Jan 2013-Jun 2014.

Results: 2,527 infants born to 2,494 HIV-infected women enrolled in the Mpepu study from May 2011 through Jun 2014, representing ~33% of HIV-infected women delivering; 85% of mothers chose to formula-feed. Overall, 1,704 (68%) mothers received 3 ARVs during pregnancy (Fig 1): 59% of the mothers prior to Jan 2013, and 78.5% from Jan 2013 on (p < 0.0001). Among women initiating 3 ARVs in pregnancy, the median duration at delivery was significantly longer for women delivering after Jan 2013 (16 weeks) vs. before Jan 2013 (12 weeks)(p < 0.0001). HIV DNA PCR was positive for 30 (1.2%) of the 2,527 infants by ~4 weeks of life. MTCT incidence was significantly lower for infants born after Jan 2013 (0.7%) vs. those born earlier (1.6%) (p = 0.04) and was only 0.6% among women treated with 3 ARVs during pregnancy. At delivery, 12 (75%) of the 16 transmitting women receiving 3 ARVs had detectable HIV RNA > 40 copies/ml (vs 27% of the 1688 non-transmitting women on 3 ARVs); only 5 (31%) of the 16 transmitting women on 3 ARVs started ≥

12 weeks before delivery, four of whom had detectable HIV RNA at delivery. For women receiving 3 ARVs, absence of viral suppression [aOR (6.7 95% CI 2.0, 22.1); p = 0.002] and < 4 weeks of ARVs before delivery [aOR 3.7(95% CI 1.1, 12.9); p= 0.04] were associated with a significantly higher risk of transmission.



Conclusions: Scale-up of universal triple-ARVs for all HIV-infected pregnant women in Botswana coincided with a fall in MTCT rates below 1%. Interventions to support earlier ART initiation and ensure virologic suppression could reduce MTCT even further.

871 Impact of Maternal Antiretroviral Regimen on Six-Month HIV-Free Survival in Botswana

Rebecca Zash[1]; Sajini Souda[2]; Chazha Hick[3]; Kelebogile Binda[3]; Sikhulile Moyo[3]; Erik van Widenfeldt[3]; Jean Leidner[4]; Joseph Makhema[3]; Mompati Mmalane[3]; Roger Shapiro[1]

[1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US; [2]University of Botswana, Gaborone, Botswana; [3]Botswana Harvard AIDS Institute, Gaborone, Botswana; [4]Harvard School of Public Health, Boston, MA, US

Background: Tenofovir/Emtricitabine/Efavirenz (Atripla) is recommended by the World Health Organization for preventing mother to child HIV transmission (PMTCT). However, no studies have evaluated MTCT and HIV-free survival during the rollout period of an Atripla-based MTCT program.

Methods: From March 2012-March 2014, HIV+ women and their infants enrolled in 5 government-run post-natal wards in Botswana. During this time, national PMTCT program transitioned from Option A [Zidovudine (ZDV) for women with CD4 ≥250 and combination antiretroviral therapy (ART) for women with CD4 <250] to Option B (Atripla for all pregnant women regardless of CD4 count). Participants were interviewed every 1-3 months by phone or home visit to assess infant HIV status and mortality. Infants were tested for HIV by dried blood spot PCR at birth by the study, and at 6 weeks old as part of routine care (and after weaning i breast-fed). The association between PMTCT strategy and 6-month HIV-free survival was assessed by logistic regression modeling controlling for maternal time on ART, maternal age and CD4 count.

Results: A total of 1499 women enrolled, representing 37% of all HIV+ women delivering during the study period. At delivery, 977 (65%) women were on ART, 410 (27%) on ZDV only, 109 (7%) on no ARVs, and 3 (0.2%) with unknown antiretroviral status. Among women on ART, 360 (37%) were receiving Atripla, 355 (36%) ZDV/3TC/NVP, 130 (13%) TDF/FTC/NVP, 47 (5%) TDF/FTC/LPV/r, 42 (4%) ZDV/3TC/LPV/r, and 43 (4%) other or unspecified ART regimens. Among 1452 (96%) infants with known HIV status at 6 months, 30 (2.1%) were HIV positive. MTCT was more common among infants born to women on ZDV-only (N=13, 3.2%) than on ART during pregnancy (N=8, 0.8%)(aOR 3.0, 95% CI 1.1, 8.1). Mortality at 6 months was similar in the pregnancy ZDV and ART exposure groups (4% and 3%, respectively), yielding an advantage in HIV-free survival of 2.6% in the pregnancy ART-exposed group (aOR 2.0, 95% CI 1.0, 4.0).

Table 1. 6-month MTCT and Infant Mortality by Maternal ART Regimen

	HIV Infection			Death			HIV infection OR Death		
	# Infants (%) N=1486*+	OR (95% CI)	aOR (95% CI)#	# Infants (%) N=1496*	OR (95% CI)	aOR (95% CI)@	# Infants (%) N=1486*+	OR (95% CI)	aOR (95%CI)^
ART	8/967 (0.8%)	1.0 (ref)	1.0 (ref)	28/977 (2.9%)	1.0 (ref)	1.0 (ref)	36/967 (3.7%)	1.0 (ref)	1.0 (ref)
ZDV-only	13/410(3.2 %)	4.1 (1.7,9.9)	3.0 (1.1,8.1)	16/410 (3.9%)	1.4 (0.7, 2.6)	1.5 (0.7, 3.3)	26/410 (6.3 %)	1.9 (1.1,3.1)	2.0 (1.0,4.0)
No ARVs	9/109 (8.3%)	10.8 (4.1,28.6)	10.2@ (5.3,38.4)	3/109 (2.9%)	1.0 (0.3,3.2)	0.9@ (0.3,4.5)	12/109 (11.0%)	3.2 (1.6,6.4)	3.0@ (1.4,6.9)
Total	30 (2.1%)			47 (3.1%)			74 (5.0%)		

*Excluding infants of 3 women with unknown ARV status during pregnancy
+Excluding 10 infants who were breastfed but did not receive HIV testing after weaning
Adjusted for CD4 count and Time on ART
@Adjusuted for CD4 count and Maternal Age
^ Adjusted for CD4 count, time on ART and Maternal Age

Conclusions: Among live-born infants followed through 6 months of life, HIV-free survival was improved when women received ART in pregnancy compared with ZDV alone, providing reassurance that the benefits of ART in pregnancy (including Atripla) are likely to exceed the risks. Further studies are needed to evaluate first-trimester Atripla exposure and risk of congenital abnormalities and stillbirths.

872 Infant Outcomes Among a Cohort of HIV-Infected Pregnant Women With and Without TB in South Africa: The Tshepiso Study

Jennifer D. Hoffmann[1]; Silvia E. Cohn[1]; **Nicole M. Salazar-Austin**[1]; Fildah Mashabela[2]; Ziyaad Waja[2]; Christopher J. Hoffmann[1]; Sanjay Lala[3]; Richard E. Chaisson[1]; Neil A. Martinson[2]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Perinatal HIV Research Unit (PHRU), Johannesburg, South Africa; [3]Chris Hani Baragwanath Hospital, Johannesburg, South Africa

Background: Perinatal morbidity in infants born to mothers with TB/HIV is higher than in infants born to mothers with HIV only. Infants of mothers with TB are more likely to suffer from perinatal death, prematurity, intrauterine growth retardation, and low birth weight. Higher rates of HIV MTCT have been reported among neonates born to mothers with HIV/TB co-infection.

Methods: Tshepiso is a prospective cohort study of HIV-infected pregnant women with active TB (cases) matched 1:2 with HIV-infected pregnant women without diagnosed active TB (controls) in Soweto, South Africa. Women are followed through pregnancy, peripartum and postpartum to record maternal and infant HIV, TB and overall clinical outcomes. All infants receive HIV prophylaxis with nevirapine (NVP) and underwent HIV DNA testing at 3-7 days, 6 weeks, and 6 and 12 months. Infants born to TB cases were referred for evaluation for congenital TB and initiation of TB prophylaxis with either isoniazid or isoniazid/rifampin. We describe here the infant clinical outcomes of the cohort.

Results: From January 2011 to June 2014, we enrolled 232 (median age 29 years) HIV-infected pregnant-women, 79 cases with active TB and 153 as non-TB controls. Of 201 total births to date, there were 4 stillbirths, 2 (3%) and 2 (1.5%) to cases and controls, respectively. Median birth weights were similar in both cases and controls, but the percentage of low birth weight (LBW, <2500 g) was 19% among cases vs 11% among controls. There was a higher rate of infant mortality among cases (6.3%) than in controls (0.77%, p<0.05). Among infants born to cases, 47 (76%) initiated TB prophylaxis within 30 days; 4 (5.8%) were diagnosed and treated for TB, vs 0 in control infants (p=0.01) There were 4 cases of MTCT of HIV transmission, 2 (3.2%) among cases and 2 (1.5%) among controls (p>0.10). 5 minute Apgar score <7 was 5% among cases and 1.5% among controls. Prematurity, congenital anomalies and growth throughout the first year of life did not differ significantly for infants born to maternal cases vs controls.

Table 1

	Cases N=64	Controls N=133	p value
Stillborn N (%)	2 (3.2%)	2 (1.5%)	p>0.10
Infant mortality (live births) N (%) (95% CI)	4 (6.3%) (1.73,15.23)	1 (0.77%) (0.02,4.2)	p=0.04
Perinatal HIV transmission N (%) (95% CI)	2 (3.2%) (0.4,11)	2 (1.5%) (0.2,5.4)	p>0.10
Infant TB N (%)	4 (5.8%)	0 (0%)	p=0.01
Low Birth Weight (< 2500 g) N (%)	12 (19%)	14 (11%)	p=0.09
Birth Weight Med [IQR] Min-max	3000 [2550,3350] 980-3800	3065 [2755,3335] 920-4425	p>0.10
Preterm (<37wks gestation) N (%)	12 (20%)	20 (17%)	p>0.10
Gestational Age at birth Med [IQR] Min-max	38 (37,40) 30-42	39 (38,40) 28-42	p >0.10
5 minute Apgar Score <7 N (%)	3 (5%)	2 (1.5%)	p>0.10

Conclusions: Our cohort revealed the TB/HIV exposed infants had significantly higher infant mortality rates than infants exposed to HIV only. There was a higher rate of MTCT among cases, but overall a low rate of transmission in the cohort. There is no difference in cases and controls at birth in terms of prematurity or median birth weight, but a trend towards higher rates of LBW and stillborn births among cases.

TUESDAY, FEBRUARY 24, 2015

Session P-T3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Option B+: Retention and Transmission

873 Early HIV Infection Rate Trends in Exposed Infants Pre- and Post-Option B+ in Mozambique

Thresia Sebastian; Serena Brusamento; Laurence Ahoua; Dario Aly; Stephen M. Arpadi; Chloe A. Teasdale; Fatima Tsiouris; Elaine J. Abrams

ICAP at Columbia University, New York, NY, US

Background: In June 2013, Mozambique adopted Option B+ which uses task shifting of ART care from clinical officers to nurses and the creation of a one-stop model at maternal/child health services for pregnant women (PW) and their HIV exposed infants (HEI). Data from ten health facilities (earliest adopters of option B+) in Nampula and Zambezia provinces were analyzed pre and post B+ to assess maternal ART uptake and early infant diagnosis.

Methods: Routinely collected aggregate data from ICAP-supported sites with antenatal care (ANC) and At Risk Child Clinic (ARCC), where HEI care is provided, were evaluated prior to and after implementation of B+. We compared uptake of care among PW and early infant (<=2 months of age) PCR positivity, using weighted paired t-tests comparing proportions across sites, one year pre and immediately post B+ implementation. Average gestational age at first ANC visit in Mozambique is around 20 weeks; therefore, delivery dates were estimated for PW and data on HEI were collected in the subsequent 4 month period. Data for the pre B+ group were collected for PW from July to Dec 2012 and for HEI from Nov 2012 to Apr 2013; in the post B+ group for PW from Jul to Dec 2013 and for HEI from Nov 2013 to Apr 2014. Proportions of early infant positivity were calculated using an estimate of the number of expected HEI calculated as 95% of HIV+ PW in ANC having live infants.

Results: 22,299 PW enrolled in care pre-B+ and 25,522 were enrolled post B+. There was no statistically significant difference between pre and post B+ periods in the proportion of PW enrolled in ANC with known HIV status (91% vs 93%, p=0.25), proportion of PW who were HIV+ (13% vs 12%, p=0.71) or proportion of HIV+ PW initiated on any ARVs (98% vs 94%,

p=0.65). The proportion of HIV+ PW that received ART increased from 37% to 94% (p=0.05). Among 1,041 HEI enrolled pre-B+ and 1,220 HEI enrolled post-B+, a significantly lower proportion of HEI tested (<=2 months of age) had a positive PCR (6% vs 4%, p=0.03). However in both periods, fewer than half the HEIs had PCR tests (41% and 46% of expected HEI).

Indicators	Pre B+	Post B+	p-value
Number of unique pregnant women (PW) enrolled in ANC services	22,299	25,522	
Total number of PW with known HIV status in ANC	20,252 (91%)	23,859 (93%)	0.25
Number of known HIV+ PW	2,690 (13%)	2,768 (12%)	0.71
Number of HIV+ PW on any ARVs	2,638 (98%)	2,605 (94%)	0.65
Number of HIV+ PW on ART	996 (37%)	2,598 (94%)	0.05
Number of expected HEI	2,556	2,630	
Number of PCR tests done on infants <=2 months of age	1,041 (41%)	1,222 (46%)	0.17
Number of PCR+ tests on infants <=2 months of age	64 (6%)	46 (4%)	0.03

Weighted paired t-test analyses of PMTCT cascade pre and post B+ implementation

Conclusions: In Mozambique, Option B+ implementation resulted in higher number of HIV+ PW initiating ART. However, significant bottlenecks in testing infants remain as less than half of HEI received early diagnostic tests. Although our finding of a lower proportion of HIV positive young infants among those tested is encouraging, more data are needed to assess the impact of option B+ on HIV-free child survival.

874 Option B+ Scale Up and Comprehensive PMTCT Service Delivery in Central Malawi

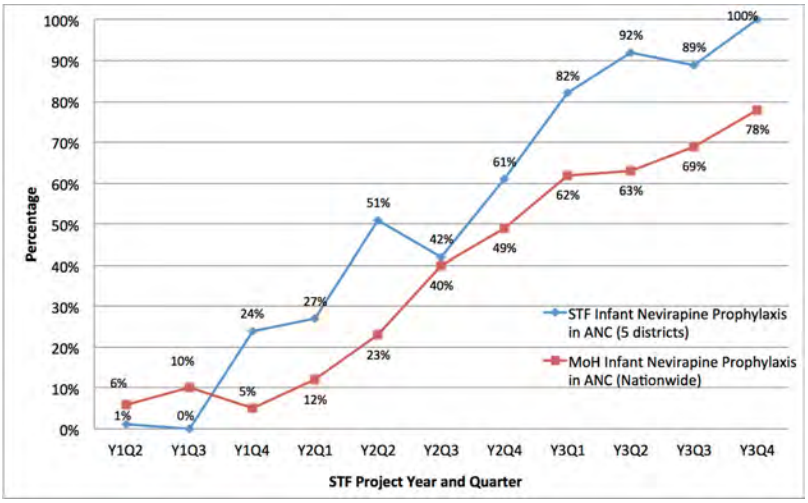
Michael E. Herce[1]; Tiwonge Mtande[2]; Frank Chimbwandira[3]; Innocent Mofolo[2]; Christine Chingondole[2]; Nora Rosenberg[4]; Kathryn Lancaster[4]; Mina C. Hosseinipour[1]; Charles M. van der Horst[1]
Safeguard the Family—Malawi Ministry of Health Partnership

[1]University of North Carolina, Lusaka, Zambia; [2]UNC Project-Malawi, Lilongwe, Malawi; [3]Malawi Ministry of Health, Lilongwe, Malawi; [4]University of North Carolina, Chapel Hill, NC, US

Background: Prior to the Ministry of Health (MoH) introducing life-long antiretroviral therapy (ART) for all HIV-positive pregnant women (Option B+) in Malawi, only one-third of HIV-positive pregnant women received ART for the prevention of mother-to-child transmission of HIV (PMTCT). We launched Safeguard the Family (STF) to support Option B+ scale up and strengthen the PMTCT continuum of care in 5 districts with 3.8 million people. We implemented facility-level quality improvement interventions to address gaps in the delivery of HIV testing and counseling (HTC), infant nevirapine (NVP) prophylaxis, and early infant HIV diagnosis (EID). We hypothesized that performance for STF districts on MoH PMTCT indicators would improve with time and outperform national averages, and that HIV-1 prevalence among exposed infants would be lower in STF districts than the national average.

Methods: We conducted a cross-sectional study using quarterly (Q) programmatic data and infant HIV-1 DNA PCR test results from STF years (Y) 1–3: Y1, April—December 2011; Y2, January—December 2012; Y3, January—December 2013.

Results: Facility-level uptake of ART, HTC, and infant NVP prophylaxis among HIV-positive pregnant women increased from baselines of 22% (n/N= 442/1,981), 66% (n/N= 32,433/48,804), and 1% (n/N= 16/1,157) to 96% (n/N= 2,046/2,121), 87% (n/N= 39,458/45,324), and 100% (n/N= 2,121/2,121), respectively, at project end (p<0.01). ART, HTC, and infant NVP prophylaxis uptake outperformed national averages by a mean of 9.8% (standard error: 2.3%), over the last 5 project quarters. STF provided interim first-time HIV-1 DNA PCR testing for 2,256 of 14,347 exposed infants (16%) enrolled in the MoH EID program in STF districts from EID program start (Y1 Q4) through Y3. Of these 2,256 infants, 79 (3.5%) tested HIV-positive. Among infants with complete EID documentation (n=615), median age at first DNA PCR testing decreased from 109 days (IQR: 57–198) in Y1/Y2 to 76 days (IQR: 46–152) in Y3 (p<0.01). During Y3 (only year with national data available for comparison), fewer HIV-exposed infants (3.6%) tested HIV-positive at first DNA PCR testing in STF districts than the national average (4.1%) (p=0.3).



Quarterly (Q) comparison of infant nevirapine prophylaxis uptake in antenatal clinics (ANC) among HIV-positive pregnant women presenting to health facilities in the Safeguard the Family (STF) catchment area versus the national average (MoH) for project years (Y) 1 to 3 (April 2011 through December 2013).

Conclusions: Delivering comprehensive PMTCT services within an Option B+ program achieved high uptake of HTC, ART, and infant NVP prophylaxis, and a low proportion of exposed infants found HIV-positive at first testing. Continued investments are needed to strengthen the PMTCT continuum of care in Malawi, particularly around EID.

875 Retention Amongst HIV-Infected Pregnant Women Initiating Lifelong Antiretroviral Treatment (Option B+) in Haiti

Jean W. Domercant[2]; Nancy Puttkammer[3]; **Lydia Lu**[1]; Kesner Francois[4]; Olbeg Desinor[5]; Reginald Jean_Louis[2]; Michelle Adler[1]; Barbara Marston[1]; Reynold Grand'Pierre[4]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]US Centers for Disease Control and Prevention (CDC), Port au Prince, Haiti; [3]International Training and Education Center for Health, Seattle, WA, US; [4]Ministry of Health of the Government of Haiti, Port au Prince, Haiti; [5]US Agency for International Development, Port au Prince, Haiti

Background: In 2012, Haiti adopted and implemented Option B+ for prevention of mother-to-child transmission of HIV (PMTCT), starting all HIV-infected pregnant women on lifelong antiretroviral therapy (ART) regardless of their CD4 count.

Methods: We conducted a retrospective analysis of retention at 6 months post-treatment initiation for all adults initiated on ART between October 2012 and July 2013, using aggregated facility-level data from iSanté, an electronic medical record system used by 89% of facilities delivering ART. Only facilities that had initiated individuals, both pregnant women and non-pregnant adults, on ART and had complete electronic data for the specified 6-month follow-up period were included in the analysis. Consistent with Ministry of Health definitions, 6 month- retention was defined as a medical appointment or pharmacy refill within 3 months of the 6 month post-ART initiation date. Using aggregate count data from facilities, we compared the cumulative incidence of 6 month retention between pregnant women and non-pregnant adults initiating ART. The Mantel-Haenszel method was used to adjust relative risk by type of health facility, sector (public, private, mixed), and location and to test for homogeneity of risk by these characteristics.

Results: Between October 2012 and July 2013, 8262 patients initiated ART at 78 facilities; 1365 (16.5%) were pregnant women and 6897 (83.5%) were men and non-pregnant women (149 of whom became pregnant after ART initiation). Overall, 87.1% of pregnant women received ART. Retention at 6 months was lower among women who initiated ART during pregnancy than in the comparison group (74.4% vs. 81.5%, adjusted RR=0.91, p<0.001). Among facilities with at least 10 patients in the Option B+ group, retention rates ranged from 43.2% (95% CI: 28.3-59.0%) to 100% (95% CI: 82.4%-100%). Differences in relative risk of retention were found by sector (p<0.001), but not by health facility type or location.

Conclusions: In the first year of Option B+ implementation, retention rates were lower and more variable for pregnant women initiating ART than for non-pregnant adults. Further investigation is needed to identify both structural and patient factors contributing to attrition among pregnant women in order to plan program interventions to strengthen retention.

THURSDAY, FEBRUARY 26, 2015

Session P-T4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Health Outcomes of HIV- and ARV-Exposed Infants, Children, and Youth

876 Malnutrition Among HIV-Exposed Uninfected Children in Botswana

Kathleen M. Powis[1]; Quanhong Lei[2]; Yvonne Chinyanga[3]; Esther Tumbare[4]; Nealia Khan[5]; Jacinta Sibiya[3]; Erik van Widenfelt[6]; Joseph Makhema[6]; Roger Shapiro[7]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]Botswana Ministry of Health, Gaborone, Botswana; [4]Elizabeth Glaser Pediatric AIDS Foundation, Harare, Zimbabwe; [5]Harvard School of Public Health, Boston, MA, US; [6]Botswana Harvard AIDS Institute, Gaborone, Botswana; [7]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US

Background: In resource limited settings, HIV-exposed infants who remain uninfected (HEU) experience higher morbidity and mortality compared with infants born HIV-uninfected women (HUU). In Botswana, where malnutrition is significantly associated with mortality in children under 5 years of age (U5), we sought to determine the prevalence between HEU and HUU children and determinants of malnutrition.

Methods: We conducted a cross-sectional study in 5 health districts in Botswana with medium to high levels of malnutrition among U5 children. Malnutrition was defined as a weight-for-length or length-for-age z-score > 2 standard deviations below the median by 2006 World Health Organization Child Growth Standards. Caregivers and U5 children were recruited while attending well-child clinics at government health facilities, where food rations for children 6 to 60 months are also dispensed. Child weight and length/height were measured by trained study staff.

Results: Of the 1,703 children enrolled, 1,109 (66.2%) were born to mothers reported to be HIV-uninfected, 432 (25.8%) to HIV-infected mothers, and 162 (9.5%) to mothers with unknown HIV status. Among HIV-exposed children, 396 (91.7%) were HEU, 7 (1.6%) HIV infected, and 29 (6.7%) were either never tested or unknown. The mean age of children did not differ between HUUs and HEUs (26 months vs 25 months; p=0.30). Prevalence of malnutrition was 26% among HUU children and 33% among HEUs (p = 0.005). Univariate differences between HEU and HUU infants are shown in Table 1. In multivariate logistic regression, birth weight (BWT) < 2.5 kg [aOR 3.3 (95% CI 2.4-4.6); p<0.0001], male child [aOR 1.5 (95% CI 1.2-1.9); p=0.002], absence of gas or electricity cooking source in the household [aOR 1.6 (95% CI 1.1-2.2); p=0.005], household food insecurity in the last month [aOR 1.3 (95% CI 1.0-1.8); p=0.05] and mother being unmarried [aOR 1.6 (95% CI 1.1-2.5); p=0.02] were associated with increased risk of malnutrition, but HEU was not [aOR 1.1 (95% CI 0.9-1.5); p=0.37].

Maternal and Infant Characteristics

Characteristic	HEU Infants (n=396)	HUU Infants (n=1,109)	p-value
Mean Maternal Age in Years [95% CI]	30.0 [29.4-30.6]	25.8 [25.5-26.2]	<0.0001
Maternal Marital Status (#, %) Single Married Divorced/Widowed	331 (85.5%) 52 (13.5%) 4 (1.0%)	932 (84.0%) 174 (15.7%) 4 (0.3%)	0.18
Household Income < 1,000 Pula/mo (#, %)	145 (37.5%)	282 (25.5%)	<0.0001
Mean Child Age in Months [95% CI]	24.9 [23.4-26.4]	25.9 [24.9-26.9]	0.30
Male Child (#, %)	213 (55.1%)	509 (45.9%)	0.002
Male Mean Birth Weight (kg) [95% CI] Female Mean Birth Weight (kg) [95% CI]	2.94 [2.87-3.02] 2.77 [2.70-2.83]	3.12 [3.07-3.16] 2.95 [2.91-3.00]	<0.0001 <0.0001
Birth Order (#, %) First Second Third Fourth Fifth or greater	78 (20.3%) 101 (26.0%) 109 (28.2%) 58 (15.0%) 41 (10.5%)	496 (44.7%) 314 (28.3%) 165 (14.9%) 73 (6.5%) 62 (5.6%)	<0.0001
No Electricity in Household (#, %)	165 (42.7%)	383 (34.5%)	0.004
No Refrigerator in Household (#, %)	197 (51.0%)	484 (43.6%)	0.01
No Tap Water in Household	258 (66.5%)	677 (61.0%)	0.05
No Electric or Gas Cooking Source in Household (#,%)	131 (33.8%)	326 (29.4%)	0.11
No toilet in household (#,%)	242 (62.5%)	642 (57.8%)	0.10
Household Food Insecurity Reported in Last Month (#, %)	112 (29.0%)	251 (22.8%)	0.01

CI = Confidence Interval; Pula represents Botswana currency; student t-test used to compare means; Chi squared test used to compare proportions

Conclusions: Low BWT and markers of poverty were associated with higher risk of malnutrition in U5 children in Botswana. In multivariate analyses, being born to an HIV infected mother did not place children at higher risk of malnutrition. However, HEU children were more likely to experience low BWT and to reside in socioeconomically deprived households. Interventions that improve BWT of HEUs and programs that address poverty eradication may minimize malnutrition among HEU children and overall in Botswana.

877 Hospitalizations Among Uninfected Children Exposed or Unexposed to HIV – A Nationwide Cohort Study

Ellen M. Larsen[1]; Marie Helleberg[2]; Sannie Nordly[3]; Nina Weis[3]; Vibeke Rosenfeldt[3]; Merete Storgaard[4]; Gitte Pedersen[5]; Isik S. Johansen[6]; Suzanne Lunding[1]; Terese L. Katzenstein[2]

[1]Nordsjællands Hospital, Hillerød, Denmark; [2]Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [3]Copenhagen University Hospital, Hvidovre, Hvidovre, Denmark; [4]Aarhus University Hospital, Skejby, Aarhus, Denmark; [5]Aalborg University Hospital, Aalborg, Denmark; [6]Odense University Hospital, Odense, Denmark

Background: Studies from resource-limited settings have shown immunological perturbations and increased risk of infectious diseases among HIV-exposed, uninfected children (HEU). Few studies from developed countries have examined morbidity in HEU. We aimed to examine risk of hospital admission among Danish HEU aged 0-4 years, compared to a matched control group of children not exposed to HIV.

Methods: In a nationwide register-based study we included all HEU born in Denmark, 2000-2010. HEU were individually matched by year of birth, quarter of birth, maternal age and ethnicity to five controls born by HIV uninfected mothers. Outcomes were risk of hospital admission (any or due to an infectious disease, non-malignant hematologic disease, or symptoms with no specific diagnosis). Incidence rate ratios were estimated using Poisson regression. Person-years at risk (PY) were calculated from 1 week after birth until the first of emigration, death, fourth birthday, first admission or end of follow-up (December 31th, 2010). Smoking during pregnancy, maternal education and number of children in household were included as covariates.

Results: In total, 260 HEU and 1300 matched controls were included. HIV-infected mothers were more likely to smoke during pregnancy (15% vs. 8%) and their infants had a lower gestational age (mean: 267 days (95% CI 264-269) vs. 278 days (95% CI 276-279)), were more likely to be delivered by Caesarean Section (68% vs. 22%) and had a lower birth weight (mean 3058g (95% CI 2974-3142) vs. 3410g (95% CI 3375-3445)). A total of 231 HEU and 893 controls had at least one admission to hospital during the study period. HEU had a three-fold increased risk of overall admissions (IRR 3.2 (95% CI: 2.8-3.7)). There was no difference in risk of admission due to infectious diseases (IRR 1.0 (95% CI 0.79-1.37)), but an increased risk of admission due to non-malignant hematologic disease (IRR 3.2 (95% CI 1.5-7.0)). The excess risk/100 PY of admission was 76.7 (95% CI 62.1-93.3) and was primarily caused by an increased risk of admission with no specific diagnosis (excess IR 58.1 (95% CI 47.9-68.3), IRR 4.5 (95% CI 3.9-5.3)) (Figure 1).

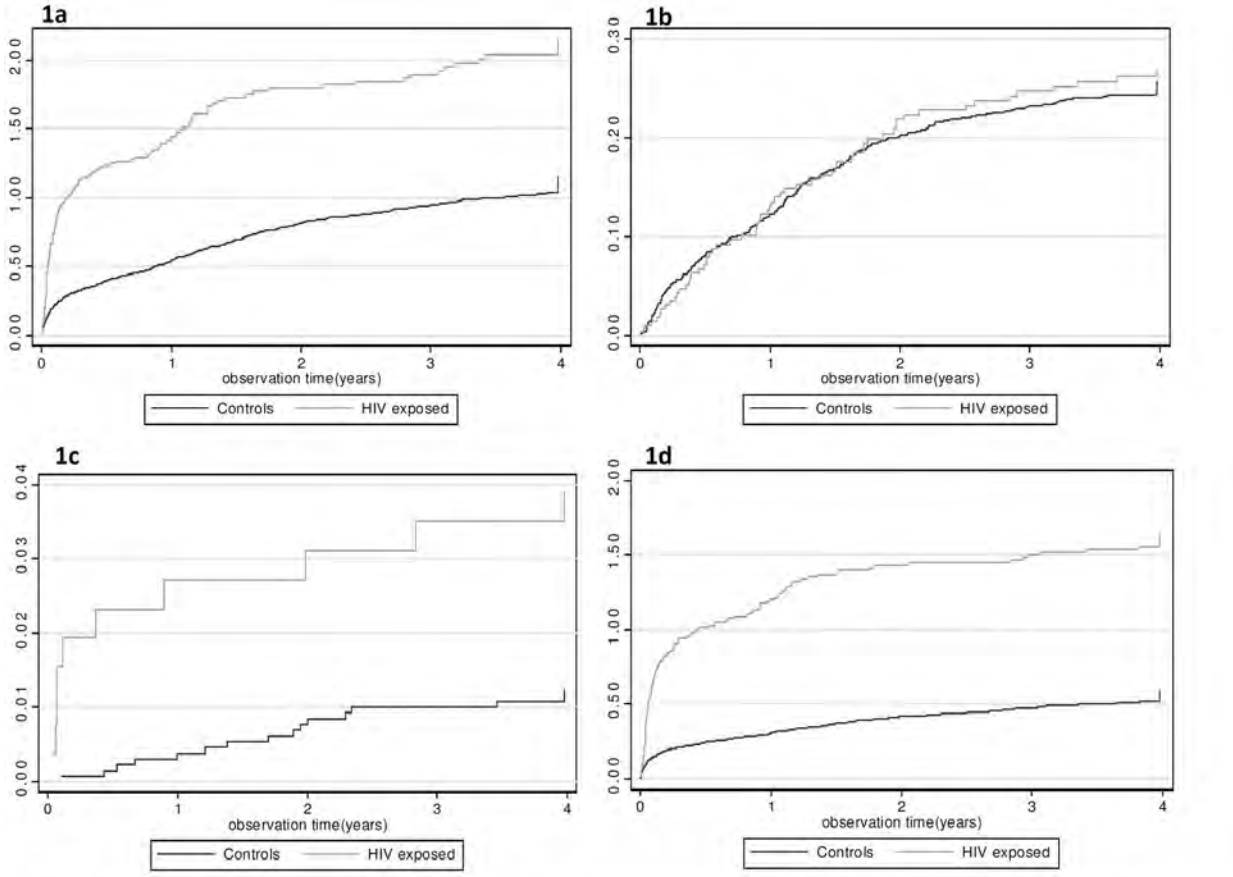


Figure 1: Time to first hospitalization for (1a) any diagnosis, (1b) infectious diseases, (1c) non-malignant hematologic diseases and (1d) symptoms with no specific diagnosis.

Conclusions: HEU had an increased risk of admission overall and of admission due to non-malignant hematologic disease. There was no increase in risk of admission due to infectious diseases. The excess risk of admission was mainly due to symptoms without specific diagnosis and may be caused by social problems rather than somatic disease related to HIV and ART-exposure.

878 Reassuring Birth Outcomes Data With Atripla Used for PMTCT in Botswana

Rebecca Zash[1]; Jennifer Y. Chen[2]; Sajini Souda[3]; Scott Dryden-Peterson[4]; Shahin Lockman[4]; Mompati Mmalane[3]; Joseph Makhema[3]; Max Essex[5]; Roger Shapiro[1]

[1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Botswana Harvard AIDS Institute, Gaborone, Botswana; [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [5]Harvard School of Public Health, Boston, MA, US

Background: Prior to introduction of tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV, Atripla), 3-drug antiretroviral treatment (ART) was associated with increased adverse birth outcomes compared with zidovudine (ZDV) used for prevention of mother-to-child HIV transmission (PMTCT). We evaluated adverse birth outcomes among pregnant women initiating Atripla vs. other ART and ZDV.

Methods: We extracted obstetric records from HIV+ women at the 2 largest maternities in Botswana from 2009-11 when Botswana National Guidelines recommended ZDV from 28 weeks gestational age (GA) for CD4 >350 and ART for CD4 <350, and again in 2013-14 after implementation of Atripla for PMTCT regardless of CD4 or GA. Outcomes included small for gestational age (SGA) (<10th% birthweight for gestational age), preterm delivery (PTD) (<37 weeks GA) and stillbirths (SB). Using logistic regression, we compared women who initiated Atripla vs. other ART (restricting analyses CD4 <350); Atripla vs. ZDV (restricting analyses to CD4 >350); and Atripla vs. any other ARV in pregnancy. Comparisons included only ARV starts before 30 wks GA and outcomes ≥30 wks GA.

Results: Data were collected on 5247 women who initiated ARVs in pregnancy: 1468 (28%) initiated Atripla; 772 (15%) other 3-drug ART combinations; 2929 (56%) zidovudine (ZDV); and 78 (1.5%) unspecified ARVs. Pregnancy CD4 count was available in 59%, and 70% started ARVs by 30 wks GA. Prevalence of adverse birth outcomes was high overall (18% SGA, 21% PTD and 3% SB), and among women initiating Atripla (12% SGA, 22% PTD and 3% SB). Compared with initiating other ART in pregnancy, Atripla had fewer SGA infants (aOR 0.4, 95% CI 0.2,0.7) and no significant differences in PTD (aOR 1.3, 95%CI 0.8,2.4) or SB (aOR 0.5, 95%CI 0.1,1.5). Compared with initiating ZDV, Atripla may have had fewer SGA infants (aOR 0.7, 95%CI 0.5,1.0) and no difference in PTD (aOR 1.0, 95%CI 0.7,1.4) or SB (aOR 1.0, 95% CI 0.4,2.1). Compared with initiating any other ARV (ART or ZDV) without CD4 restriction, Atripla had fewer SGA infants (aOR 0.6, 95% CI 0.4,0.8) and no difference in PTD (aOR 1.0, 95%CI 0.8,1,3) or SB (aOR 0.8, 95% CI 0.4,1.5).

Table 1: Adverse Birth Outcomes among women who initiated TDF/FTC/EFV compared with Other ARV regimens in Pregnancy

	CD4 <350[&]			CD4>350[&]			All CD4 Strata[~]		
	Initiated Atripla in pregnancy N=242	Initiated Other 3-drug ART in pregnancy+ N=267	aOR (95%CI)	Initiated Atripla in pregnancy N=347	Initiated ZDV in pregnancy N=876	aOR (95% CI)	Initiated Atripla in Pregnancy N=1092	Initiated any other ARV in pregnancy N=2466	aOR (95%CI)
Stillbirth[$]	5(2.1%)	13(4.9%)	0.5 (0.1,1.5)	9 (2.6%)	24(2.7%)	1.0 (0.4,2.1)	20 (1.8%)	77 (3.1%)	0.8 (0.4,1.5)
Preterm[$$] <37wks	46 (19.0%)	52(19.5%)	1.3 (0.8,2.4)	60 (17.3%)	150(17.1%)	1.0 (0.7,1.4)	197 (18.0%)	517 (21.0%)	1.0 (0.8,1.3)
Small for Gestational Age[$$$]	26 (10.7%)	55 (20.6%)	0.4 (0.2,0.7)	53 (15.3%)	181(20.7%)	0.7 (0.5,1.0)	131(11.6%)	513 (20.8%)	0.6 (0.4,0.8)

&Women with unknown CD4 count excluded from analysis
~Analysis Includes women with unknown CD4 count
+ Other 3-drug ART regimens included ZDV/lamivudine (3TC)/nevirapine (NVP) (36%), unspecified ART (38%) which was likely mostly ZDV/3TC/NVP given National ARV guidelines, ZDV/3TC/Lopinavir/ritonavir (19%), TDF/FTC/NVP(4%), and other ART (3%).
$ Among all women initiating Atripla (unrestricted by GA) total SB = 39/1468 (2.7%). Among all women initiating other ART (unrestricted by GA),total SB = 33/772 (4.3%). Among all women initiating ZDV (unrestricted by GA) total SB = 76/2929 (2.6%)
$$ Among all women initiating Atripla (unrestricted by GA) total PTD = 219/1468 (21.7%). Among women initiating other ART (unrestricted by GA), total PTD = 177/772 (22.9%). Among women initiating ZDV (unrestricted by GA), total PTD = 601/2929 (20.5%).
$$$ Among all women initiating Atripla (unrestricted by GA), total SGA = 178/1468 (12.1%). Among all women initiating other ART (unrestricted by GA), total SGA = 155/772 (20.1%). Among women initiating ZDV (unrestricted by GA), total SGA = 588/2929 (20.1%)

Conclusions: Adverse birth outcomes remain high among HIV+ women in Botswana. Atripla appeared at least as safe as other ARVs started by 30 weeks gestation, and was associated with fewer SGA infants. Larger studies with Atripla exposures from conception are needed to evaluate earlier pregnancy outcomes and neural tube defects.

879 Growth and Bone Markers in Malawian Infants Pre- and Postnatally Exposed to Tenofovir

Giuseppe Liotta[2]; Marco Floridia[1]; **Mauro Andreotti**[1]; Haswell Jere[3]; Clementina Galluzzo[1]; Sandro Mancinelli[2]; Maria Cristina Marazzi[4]; Stefano Vella[1]; Marina Giuliano[1]; Leonardo Palombi[2]

[1]Istituto Superiore di Sanità, Rome, Italy; [2]University of Tor Vergata, Rome, Italy; [3]Community of S.Egidio, Blantyre, Malawi; [4]Lumsa University, Rome, Italy

Background: Tenofovir (TDF) is known to affect bone metabolism in HIV-infected patients. Prenatal and postnatal exposure to tenofovir might therefore affect negatively bone metabolism and postnatal growth in infants from mothers who received tenofovir in pregnancy and continue treatment after delivery while breastfeeding. No data are available on bone metabolism markers and infant growth status in this population.

Methods: We studied 103 mother/child pairs enrolled in Malawi in an Option B-Plus program. All women received tenofovir+lamivudine+efavirenz in pregnancy (started at a median gestational time of 23 weeks) and during a breastfeeding time of up to 2 years. Bone markers and growth status was assessed in infants at 6 and 12 months of age, measuring serum Bone-specific alkaline phosphatase (BAP), as a specific marker of bone formation, and C-terminal telopeptide of type I collagen (CTX), as a bone resorption marker. Gender-adjusted weight-for-age z-scores (WAZ) and height-for-age z-score (HAZ) were calculated using the WHO standards (2006).

Results: Median (IQR) BAP levels in infants were 278 (117-371) IU/ml at 6 months and 186 (82-287) IU/ml at 12 months, respectively. Corresponding median CTX levels at the same times were 320 (225-565) ng/L and 590 (260-865) ng/L, respectively. Levels of bone markers showed no differences by gender or by presence of severe weight or height reduction (WAZ or HAZ <10° WHO percentile), both at 6 and 12 months. Mean (SD) WAZ and HAZ were -0.77 (1.33) and -1.19 (1.25) at 6 months and -0.97 (1.22) and -1.40 (1.23) at 12 months, respectively.

Conclusions: Based on published data, BAP and CTX levels showed no evidence of a negative impact on bone metabolism, with BAP levels slight higher and CTX levels lower compared to values previously reported in general pediatric populations. Although the infants were clearly below the WHO standards for both weight and for height measures, we found no evidence of a link between growth impairment and bone markers levels. Further studies that also take into account the potential role of inadequate nutritional intake in this setting are needed.

880 Lower Insulin, Acylcarnitines, and Branch-Chain Amino Acids in HIV-Exposed Infants

Jennifer Jao[1]; Brian Kirmse[2]; Chunli Yu[3]; Fanny Epie[4]; Emmanuel Nshom[4]; Rhoda Sperling[5]; Elaine J. Abrams[6]; Derek LeRoith[7]; Mitchell Geffner[8]; Irwin Kurland[9]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, US; [2]Children's National Health System, Washington, DC, US; [3]Icahn School of Medicine at Mount Sinai, New York, NY, US; [4]Cameroon Baptist Convention Health Services, Bamenda, Cameroon; [5]Icahn School of Medicine at Mount Sinai, New York, NY, US; [6]ICAP at Columbia University, New York, NY, US; [7]Icahn School of Medicine at Mount Sinai, New York, NY, US; [8]Keck School of Medicine at University of Southern California, Los Angeles, CA, US; [9]Albert Einstein College of Medicine, New York, NY, US

Background: *In utero* HIV/ARV exposure can cause mitochondrial dysfunction and may affect fetal metabolic programming. No studies have evaluated intermediary energy metabolism and insulin levels in HIV-exposed (HEU) and -unexposed (HUU) uninfected infants in Africa.

Methods: We measured preprandial insulin levels at 6 weeks of life from dried blood spots (DBS) via direct sandwich ELISA technique and calculated Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) scores in Cameroonian HEU and HUU infants from 2011- 2014. Demographic, clinical, and *in utero* and postnatal ARV exposure data were collected. Acylcarnitines (ACs) and branch-chain amino acids (BCAAs) were measured via tandem mass spectrometry. We used principal component analysis (PCA) to consolidate the ACs and BCAAs into 5 uncorrelated clusters. We used linear regression models to assess the association of *in utero* HIV/ARV exposure and infant insulin while adjusting for confounders and PCA-derived AC/BCAA component scores.

Results: Of 366 infants, 156 were HEU. Mothers of HEU infants were older (30 vs. 28 years, $p<0.01$), more often single (23 vs. 12%, $p=0.02$), and more likely to have had only primary/secondary education levels ($p=0.04$). Maternal body mass index (BMI), blood pressure, and gestational diabetes rates did not differ between groups. Birth weight *z* scores, prematurity rates, and weight-for-age *z* (WAZ) scores also did not differ, but length-for-age *z* and head circumference-for-age *z* scores were lower in HEU infants at 6 weeks (0.42 vs. 0.91, $p=0.05$ & 0.30 vs. 0.75, $p=0.01$ respectively). Median insulin levels and HOMA-IR scores were lower in HEU infants (3.6 vs. 4.9 μIU/mL, $p<0.01$ & 0.87 vs. 1.12, $p<0.01$ respectively). Two PCA components differed significantly between groups: Component 3 comprised of AC C2, C3, C4, C5, C6, C4OH, C5OH, C3DC, C4DC, C5DC, and C10 ($p=<0.01$) and Component 5 comprised of BCAA (leucine, isoleucine, valine, $p=0.04$). In multivariate modeling HEU status remained associated with lower infant insulin [$\beta=(-0.06)$, $p=0.04$). Furthermore, infant WAZ ($\beta=0.04$, $p<0.01$), Component 3 ($\beta=0.06$, $p<0.01$) & Component 5 ($\beta=0.03$, $p=0.02$) were associated with higher insulin levels.

Table. Linear Regression Model for Infant Insulin at 6 weeks

Risk Factor	Coefficient	*p* value
Maternal HIV Status		
HIV exposed uninfected	-0.058	*0.041*
HIV unexposed uninfected	0	
Maternal age, per year	-0.001	*0.761*
Highest Level of Education		
Secondary School or lower	-0.026	*0.326*
High School or higher	0	
Maternal gestational diabetes status		
Gestational diabetes	0.061	*0.280*
No gestational diabetes	0	
Infant Gender		
Female	-0.004	*0.873*
Male	0	
Low Birth Weight (<1500 g)	0.036	*0.614*
Preterm Birth (<37 weeks)	0.009	*0.817*
Infant weight-for-age *z* score at 6 weeks	0.043	*<0.001*
Component 1	-0.005	*0.713*
Component 2	-0.006	*0.696*
Component 3	0.059	*<0.001*
Component 4	0.013	*0.325*
Component 5	0.031	*0.019*

Conclusions: Compared to HUU, HEU infants have lower insulin levels at 6 weeks of life. Distinguishing clusters of short-chain ACs and BCAAs were also associated with infant insulin levels. Future studies should determine the significance of these early metabolic changes on later health and morbidity.

881 No Effect of Maternal HIV and In-Utero cART on Infant Leukocyte Telomere Length

Abhinav Ajaykumar[1]; Hugo Soudeyns[2]; Fatima Kakkar[2]; Jason Brophy[3]; Ari Bitnun[4]; Ariane Alimenti[1]; Deborah Money[1]; Arianne Albert[5]; Hélène C. Côté[1]
On behalf of the CIHR Team in Cellular Aging and HIV Comorbidities in Women and Children (CARMA)

[1]University of British Columbia, Vancouver, Canada; [2]Université de Montréal, Montreal, Canada; [3]University of Ottawa, Ottawa, Canada; [4]University of Toronto, Toronto, Canada; [5]Women's Health Research Institute, Vancouver, Canada

Background: Maternal combination antiretroviral therapy (cART) in pregnancy could have long-term effects on HIV-exposed uninfected (HEU) children. Some antiretrovirals and HIV proteins inhibit telomerase, the enzyme that elongates telomeres. We previously reported shorter leukocyte telomere length (LTL) in HIV+ adults compared to HIV- controls but saw no association with duration of cART. Among children (0-19y) and infants (0-3d) however, no difference in LTL was seen between HIV+, HEU and HIV-unexposed uninfected (HUU) controls, although among HIV+ children, being on cART was associated with longer LTL, and HEU cord blood trended toward shorter LTL. As LTL is a marker of cellular aging and has been linked to age-related morbidities, our objective was to compare HEU and HUU infant LTL at birth and over the first six years of life in this larger cohort and investigate any relationship to cART exposure.

Methods: Of 324 HEU children aged 0-3y enrolled in the CARMA cohort study, most (n=215) had ≥2 blood samples collected. HUU controls (0-3y, n=308) had a single blood sample each. LTL was measured on whole blood DNA via monochrome multiplex qPCR. A subset of 0-3y HEU and HUU children were randomly age- and sex-matched 1:1. Factors associated with LTL were investigated using linear regression modeling.

Results: A cross-sectional analysis of LTL at birth (0-3d) in 115 HEU (56% male) and 91 HUU (54% male) infants considered HIV exposure status, infant sex, gestational age, maternal age, race/ethnicity and smoking ever in pregnancy as explanatory variables. Male sex was associated with shorter LTL at birth (p=0.02), and there was a significant interaction between HEU/HUU status and maternal smoking (p=0.009) with the latter being associated with longer LTL in HUU and shorter LTL in HEU. Among HEU, neither duration of cART exposure *in utero* nor type of cART was related to birth LTL. There was no difference in LTL attrition rate during the first six weeks of life. Furthermore, among age and sex-matched children (n=214:214), LTL attrition rate was not significantly different between groups (p=0.69), but there was a significant sex by age effect with males having slower attrition than females (p=0.03).

Conclusions: These results further support that exposure to maternal HIV/cART *in utero* does not affect infant LTL, a reassuring finding. It is unclear how exposure to maternal smoking affects LTL; the opposite associations seen here may represent a sampling artifact or a surrogate for other factors.

882 Long-Term Effects of In Utero ARV Exposure on Cardiac Function in HIV-Exposed Uninfected Youth

Vitor C. Guerra[1]; Erin Leister[2]; Paige L. Williams[2]; Steven E. Lipshultz[3]; Russell Van Dyke[1]; Rohan Hazra[4]; Steven D. Colan[5]

[1]Tulane University, New Orleans, LA, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]Wayne State University School of Medicine, Detroit, MI, US; [4]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US; [5]Boston Children's Hospital, Harvard Medical School, Boston, MA, US

Background: Most evaluations of cardiac function in children born to mothers with HIV have focused on infants and children. However, as combination antiretroviral (ARV) regimens become more widely used during pregnancy, potential long-term cardiac effects of in utero ARV exposures warrant monitoring. We evaluated the association of *in utero* exposure to highly active antiretroviral therapy (HAART) with left ventricular (LV) function and structure in HIV-exposed uninfected (HEU) children.

Methods: Echocardiographic measures of left ventricular (LV) systolic and diastolic function and cardiac structure were obtained in HEU children aged 6 years and older enrolled in the PHACS Surveillance Monitoring of ART Toxicities (SMARTT) Study. Echocardiographic Z-scores were calculated using normative data from an established reference cohort of healthy children from Boston Children's Hospital, with adjustment for age and body-surface area, as appropriate. We used adjusted linear regression models and latent variable models to compare Z-scores for echocardiographic measures from HEU children exposed *in utero* to HAART with those exposed to non-HAART antiretroviral (ARV) therapy, adjusting for demographic and maternal health characteristics including substance use.

Results: 174 HEU subjects with echocardiograms and maternal ARV information were included (mean age at echocardiogram=10.9 years; 48% male, 56% Black non-Hispanic). We observed no differences in Z-scores for LV systolic function measures for those exposed *in utero* to HAART (39%) compared to HAART-unexposed in either unadjusted or adjusted models. In adjusted models, those exposed to HAART, as compared to HAART-unexposed, had significantly lower mitral late diastolic inflow velocities (adjusted mean Z-score=0.00 vs 0.52, p=0.04), and significantly higher adjusted mean LV mass-to-volume ratio Z-scores (adjusted mean Z-score=0.47 vs 0.11, p=0.03). There were no associations observed between ARV exposure in the first trimester and any LV systolic or diastolic echocardiogram measure.

Conclusions: Uninfected youth with perinatal exposure to HAART had no difference in LV systolic function. However, small but significant differences in LV diastolic function and cardiac structure were observed, suggesting that continued monitoring for cardiac outcomes is warranted in this population.

THURSDAY, FEBRUARY 26, 2015

Session P-T5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Coinfections Among HIV-Exposed Infants and Children

883 Burden of Malaria in a Birth Cohort of HIV-Exposed Ugandan Infants

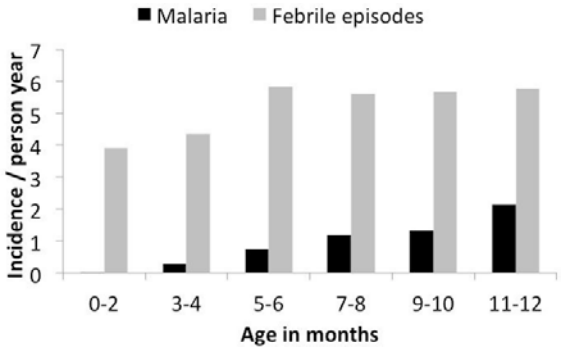
Abel Kakuru[2]; Paul Natureeba[2]; Albert Plenty[1]; Edwin Charlebois[1]; Deborah Cohan[1]; Tamara Clark[1]; Diane Havlir[1]; Moses R. Kamya[3]; Grant Dorsey[1]; **Theodore Ruel**[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Makerere University-University of California, San Francisco Research Collaboration, Kampala, Uganda; [3]Makerere University College of Health Sciences, Kampala, Uganda

Background: HIV-exposed infants suffer high mortality in the first year of life, but accurate data on the burden of malaria are lacking. We evaluated the incidence of febrile illnesses and malaria in a birth cohort born to HIV-infected women living in a hyper-endemic area of rural Uganda where the incidence of malaria in a contemporaneous cohort of HIV-unexposed infants aged 6-12 months was over 5 episodes/person-year.

Methods: In the PROMOTE trial (NCT00993031), HIV-infected pregnant women were randomized to either efavirenz- or lopinavir- based therapy. Infants were given insecticide treated bednets at birth, cotrimoxazole prophylaxis at 6 weeks of age, and followed for all their health care needs in the study clinic until 12 months of age. All febrile episodes were evaluated with blood smears for malaria and if present, treated. Risk factors for malaria were assessed using generalized estimating equations.

Results: Of 361 infants born to 377 HIV-infected mothers and surviving beyond 24 hours, 19% were low birth weight (< 2500 gm), 17 were pre-term (< 37 weeks), and 34% had evidence of placental malaria by histopathology. In 305 patient-years (py) of follow up, there were 1561 febrile episodes (5.1/py) and 265 episodes of malaria (0.87/py). The incidence of febrile illnesses increased modestly after 4 months of age (Figure). In contrast, the incidence of malaria incidence increased dramatically over the first year of life (p<0.001, Figure) with only 2 episodes of malaria in infants under 2 months of age, neither of whom had started cotrimoxazole. The proportion of febrile illnesses that were malaria increased from < 1% at 0 -2 months of age to over 37% by 11-12 months of age. Low birth weight, prematurity, maternal study arm, and placental malaria were not significantly associated with malaria during the first year of life. There were no episodes of WHO-classified complicated malaria, 6 deaths (none from malaria), and 2 cases of HIV transmission.



Conclusions: HIV-exposed infants living in a hyper-endemic area who had access to cotrimoxazole prophylaxis and prompt malaria treatment experienced lower rates of malaria than HIV-unexposed infants, with no complicated malaria or malaria mortality. These results underscore the importance of accurate malaria testing and the consideration of non-malarial infectious etiologies in reducing the morbidity and mortality of HIV-exposed infants, especially those < 6 months of age.

884 CMV Transmission From HIV-infected Women Randomized to Formula Versus Breastfeeding

Barbra Richardson[1]; Grace John-Stewart[1]; Vincent Emery[2]; Claire Atkinson[4]; Ruth Nduati[3]; Kristjana H. Ásbjörnsdóttir[1]; Julie M. Overbaugh[5]; Michael Boeckh[5]; **Jennifer A. Slyker**[1]

[1]University of Washington, Seattle, WA, US; [2]University of Surrey, Guildford, United Kingdom; [3]University of Nairobi, Nairobi, Kenya; [4]University College London, London, United Kingdom; [5]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US

Background: Cytomegalovirus (CMV) is associated with infant HIV disease progression. We compared rates of CMV infection between breastfed (BF) and formula fed (FF) infants and determined the relative proportion of infections attributable to congenital, intrapartum, breast milk, and other modes of transmission.

Methods: Between 1993-1998 pregnant, HIV-infected women from Nairobi, Kenya, were randomized at 32 weeks gestation to breastfeed or formula feed their infants in a study designed to compare rates of vertical HIV transmission (Nduati et al, JAMA 2000). Blood was collected serially over 2 years. We evaluated CMV acquisition as an additional study

endpoint using real-time quantitative PCR and serology in stored specimens. Timing of CMV infection was compared between arms using Kaplan Meier and Cox proportional hazards models. In utero transmission was defined as CMV DNA detection within 2 weeks of birth and intrapartum transmission was defined as first CMV detection between 2 and 6 weeks. Non-breastfeeding transmissions were defined as those with first CMV DNA detection after the 6-week study visit in FF infants, and infections through breast milk were estimated as the excess infections between the BF and FF infants after the 6-week study visit.

Results: A subset of 138 infants randomized to breastfeed and 134 randomized to formula feed were assessed for CMV infection. Baseline characteristics including maternal HIV disease status and sociodemographics were similar between arms. BF infants acquired CMV at an earlier median age (4.26 months, SD=0.97) than FF infants (9.87 months, SD=1.27; log rank p<0.001) and the probability of infection by 1 year was 0.89 (SD=0.03) in the BF and 0.69 (SD=0.05) in the FF infants (p<0.001; Figure). Overall, breastfeeding was associated with a 1.67-fold increased risk of infant CMV infection (hazard ratio (HR): 1.67, 95% CI: 1.24-2.23, p=0.001) and was independent of infant HIV infection status (multivariate HR: 1.61, 95% CI: 1.20-2.16, p=0.002). Among BF infants assessed over 1 year, we estimated 9% of CMV infections occurred in utero, 23% intrapartum, 36% through breastfeeding, and 31% through non-breast milk postpartum modes such as saliva and urine.

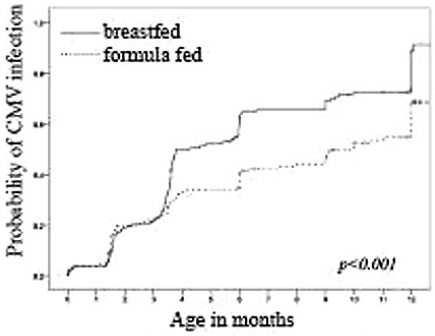


Figure. Kaplan-Meier survival curves showing CMV acquisition in infants randomized to breastfeeding vs formula.

Conclusions: More than a third of CMV infections in BF infants of HIV-infected mothers occur through breast milk transmission. Vaccine strategies for this population will need to consider the very high rate of transmissions during the first months of life.

885 Is the Prevalence of *M. tuberculosis* Infection Higher in HIV-Exposed Children?

Palwasha Y. Khan[1]; Katherine L. Fielding[1]; Dominic Mulawa[2]; Regina Chiumya[2]; Themba Mzembe[2]; Olivier Koole[1]; Judith R. Glynn[1]; Amelia C. Crampin[1]

[1]*London School of Hygiene and Tropical Medicine, London, United Kingdom;* [2]*Karonga Prevention Study, Karonga, Malawi*

Background: The effect of HIV exposure on the risk of *Mycobacterium tuberculosis (M.tb)* infection and tuberculosis (TB) in children is not well understood. HIV-exposed uninfected children have an increased risk of morbidity and mortality in sub-Saharan Africa. In high HIV/TB burden settings increased susceptibility and/or exposure to *M.tb* in children born to HIV-positive mothers may contribute to ill health despite PMTCT.

Study hypothesis: Prevalence of *M.tb* infection is higher in HIV-exposed children compared to HIV-unexposed

Methods: *Setting:* Demographic surveillance site, northern Malawi. Adult HIV prevalence ~8%

Eligibility: Children aged 2 to 5 years

Dates: January 2012 - July 2014

Design and procedures: Cross-sectional study of tuberculin skin testing (TST) (2TU of purified protein derivative RT23). A positive TST was defined as induration ≥15mm. Maternal HIV sero-status, BCG vaccination, household socio-economic status, household contact with a TB case and smear-positive TB notification data were available from related studies. Children whose mothers were known to be HIV-positive at the time of delivery were defined as HIV-exposed. Children <2 years were not included to minimise misclassification due to BCG-attributable induration.

Results: 3707 children were eligible, of whom 3302 (89.0%) were enrolled. Of these, 3296 had a TST placed and read within 48-72hrs. 106 (3.2%) had a TST≥10mm and 35 (1.1%) had a TST≥15mm. 92/3296 (2.8%) of children were classified as HIV-exposed and 469 (14.2%) had unknown HIV exposure status. Documented BCG vaccination date was available for 2673 (81.1%). See table. Random effects logistic regression analysis showed that the odds of a positive TST was 4 times higher in children who had been exposed to HIV before birth, adjusting for age and community *M.tb* exposure [aOR 4.1 (1.2 – 14.0, p=0.024)].

Table. Univariable and multivariable analysis of risk factors associated with TST≥15mm

Risk factor	TST≥15mm (N=3296) n/N (row %)	Unadjusted OR (95% CI)	p value	Model 1* Adjusted OR (95% CI) (N=3296)	p value	Model 2# Adjusted OR (95% CI) (N=3296)	p value
HIV exposure status							
Unexposed	24/2727 (0.9)	1		1		1	
Exposed	3/92 (3.3)	3.8 (1.1 - 12.8)	0.03	**4.1 (1.1 - 14.0)**	0.02	**3.9 (1.1 – 13.2)**	0.03
Unknown	8/478 (1.7)	2.0 (0.9 – 4.4)	0.10	1.8 (0.8 – 4.1)	0.15	1.7 (0.8 – 3.9)	0.20
Age (years)							
2.0-2.9	8/1093 (0.7)						
3.0-3.9	12/1140 (1.1)	1.4* (0.9 – 2.1)	0.13	1.4* (0.9 – 2.2)	0.10	1.4* (0.9 – 2.2)	0.10
4.0-4.9	15/1063 (1.4)						
Community *M.tb* exposure (av. smear-positive TB notification rate per 100,000 population per residential area)^							
<20	4/828 (0.5)						
20 - 39	18/1666 (1.1)	1.7* (1.1 – 2.8)	0.03	1.7* (1.0 – 2.8)	0.04	1.7* (1.1 – 2.8)	0.03
≥40	13/802 (1.6)						
Household TB contact during child's lifetime							
No	33/3271 (1.0)	1				1	
Yes	2/25 (8.0)	8.5 (1.9 – 37.7)	0.005			7.3 (1.6 – 33.1)	0.01

*Adjusted for all risk factors in model
* Assuming linear trend
^21 geographically-defined residential areas

Table showing univariable and multivariable analysis of risk factors associated with TST positivity

Conclusions: This study shows that children aged 2 to 5 years born to HIV-positive women have a 4-fold increased risk of *M.tb* infection compared to HIV-unexposed children. This increased risk may be even higher than measured as HIV-infected children may not react to TST. Further research is required to investigate whether observed increased risk in HIV-exposed children is due to increased susceptibility to *M.tb* and/or increased *Mtb* exposure. HIV and TB are family diseases and improved tuberculosis control in the long-term will only be achieved with better integration between HIV, TB, maternal and child health services in high-burden settings.

TUESDAY, FEBRUARY 24, 2015

Session P-T6 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

ART Adherence, Adverse Effects, and Retention Among Pregnant Women and Infants

886 ARV Adherence Associated with Reduced Breastmilk HIV Viral Load and HIV Transmission

Nicole L. Davis[4]; **William C. Miller**[4]; Michael G. Hudgens[4]; Charles S. Chasela[1]; Dorothy Sichali[2]; Julie A. Nelson[4]; Joseph Rigdon[4]; Sascha R. Ellington[3]; Athena P. Kourtis[3]; Charles M. van der Horst[4]
BAN study team

[1]University of Witswatersand, Johannesburg, South Africa; [2]UNC Project-Malawi, Lilongwe, Malawi; [3]US Centers for Disease Control and Prevention (CDC), Atlantaq, GA, US; [4]University of North Carolina, Chapel Hill, NC, US

Background: To prevent mother-to-child HIV transmission, antiretroviral (ARV) interventions have been used to reduce HIV viral replication in breastmilk and maternal blood. Achieving and maintaining viral suppression relies on adherence to ARV regimens.

Methods: A case cohort study was conducted using data from the Breastfeeding, Antiretrovirals and Nutrition study to comprehensively assess the role of adherence on transmission. We included mothers randomized to 28 weeks of postpartum maternal ARV or infant nevirapine who had ≥1 plasma or breastmilk specimen available between 2-24 weeks postpartum. Among these, we included all mothers who transmitted HIV to their infants between 2-28 weeks and 15% of mothers who did not transmit HIV by 28 weeks (n=31 and 232, respectively). Adherence was measured using maternal ARV pill counts and categorized as poor (0-80%), partial (81-98%) and near perfect (>98%). Associations between maternal ARV adherence and breastmilk HIV RNA concentration were assessed using mixed effects models. Cox models were used to estimate associations between breastmilk HIV RNA concentration and breastmilk HIV transmission between 2-28 weeks. A Monte Carlo simulation was then conducted to estimate the number of transmissions that would have been averted between 2-28 weeks postpartum if all mothers randomized to maternal ARVs (n=848) had been 100% adherent.

Results: Mean adherence was 88% [median 0.96, IQR 0.86-1.00] among mothers in the maternal ARV arm. Having at least partial maternal ARV adherence significantly reduced the odds of having detectable (>40 copies/ml) breastmilk HIV RNA (partial vs. poor OR 0.23, 95%CI 0.08-0.67; near perfect vs. poor OR 0.36, 95% CI 0.16-0.81). Detectable breastmilk HIV RNA was associated with 7.4 (95% CI 3.2-17.1) times the adjusted relative rate of breastmilk HIV transmission. Among mothers who transmitted HIV to their infant, all had at least one plasma viral load >100 copies/ml. Using Monte Carlo simulation, if all mothers randomized to maternal ARVs had been 100% adherent we estimated a 36% decrease in HIV transmissions between 2-28 weeks postpartum, compared to transmissions estimated under observed adherence [transmissions under perfect adherence: 14, 95% prediction interval (PI) 7-21; transmissions under observed adherence: 22, 95% PI 13-32].

Conclusions: Lower breastmilk RNA was associated with better adherence and lower risk of transmission. Maintaining plasma viral load <100 copies/ml may be effective at preventing breastmilk transmission.

887 Peripartum Hair Levels of Antiretrovirals Predict Viral Suppression in Ugandan Women

Catherine A. Koss[1]; Peter Bacchetti[1]; Deborah Cohan[1]; Paul Natureeba[1]; Howard Horng[1]; Tamara Clark[1]; Edwin Charlebois[1]; Moses R. Kamya[2]; Diane Havlir[1]; Monica Gandhi[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Makerere University College of Health Sciences, Kampala, Uganda

Background: Combination antiretroviral therapy (ART) is recommended for all HIV-infected pregnant women worldwide. Adequate antiretroviral (ARV) exposure is critical to maintain maternal health and reduce transmission to infants and partners. Hair concentrations are a non-invasive measure of cumulative ARV exposure that integrate adherence and pharmacokinetics and are the strongest predictor of viral suppression in large prospective cohorts. However, hair concentrations of ARVs have not yet been examined in the peripartum period.

Methods: The PROMOTE trial (NCT00993031) enrolled HIV-infected, ART-naïve pregnant Ugandan women at 12-28 weeks gestation who were randomized to initiate lopinavir (LPV) or efavirenz (EFV)-based ART. Small hair samples were collected at 30-34 weeks gestation and 12 weeks postpartum. EFV and LPV hair concentrations were measured via liquid chromatography/tandem mass spectrometry. Multivariate logistic regression models examined predictors of viral suppression (HIV-1 RNA <400 c/ml) at delivery and 24 weeks postpartum in women on ART for ≥6 weeks. Potential predictors included log-transformed ARV hair concentration (interpolated for delivery), age, pretreatment HIV-1 RNA, self-reported adherence, and time on ART.

Results: Among 325 women, mean age was 30 years (SD 5.4) and median CD4 cell count was 366 cells/mm^3 (IQR 270-488) at ART initiation. Median time on ART at delivery was 17 weeks (IQR 14-21). Mean self-reported adherence was >97% in each arm. Viral suppression was achieved by 98% (EFV) and 87% (LPV) at delivery and 93% (EFV) and 91% (LPV) at 24 weeks postpartum. In multivariate models including self-reported adherence and pretreatment HIV-1 RNA (Table), ARV hair concentrations were the strongest predictor of viral suppression at delivery (EFV: aOR 1.86 per doubling in concentration [95% CI: 1.14-3.1], p=0.01; LPV: aOR 1.90 [95% CI: 1.33-2.7], p=0.0004) and 24 weeks postpartum (EFV: aOR 1.81 [95% CI: 1.22-2.7], p= 0.003; LPV: aOR 1.53 [95% CI: 1.05-2.2], p=0.03).

Multivariate Analysis of Predictors of Viral Suppression at Delivery and 24 Weeks Postpartum

	Delivery		24 Weeks Postpartum	
Variable	**aOR (95% CI)**	***P***	**aOR (95% CI)**	***P***
Efavirenz				
ARV hair concentration, per doubling	1.86 (1.14-3.1)	**0.01**	1.81 (1.22-2.7)	**0.003**
Self-reported adherence, per 10% of prescribed dose	1.00 (0.29-3.4)	1.00	*	*
Pretreatment HIV-1 RNA, per 10-fold increase			0.38 (0.14-1.05)	0.06
Lopinavir				
ARV hair concentration, per doubling	1.90 (1.33-2.7)	**0.0004**	1.53 (1.05-2.2)	**0.03**
Self-reported adherence, per 10% of prescribed dose	2.2 (0.53-8.9)	0.28	3.3 (0.88-12.4)	0.56
Pretreatment HIV-1 RNA, per 10-fold increase	0.25 (0.11-0.54)	**0.0005**		

aOR, adjusted odds ratio. ARV, antiretroviral.
* There was too little variation in self-reported adherence to permit a meaningful estimate.

Conclusions: We examined hair concentrations of ARVs in relation to virologic outcomes in pregnant and postpartum women for the first time. Hair concentrations of EFV and LPV were the strongest predictors of viral suppression at delivery and 24 weeks postpartum, surpassing self-reported adherence and pretreatment HIV-1 RNA. Hair concentrations are an innovative tool for measuring long-term ARV adherence and exposure and may be helpful to monitor women during the critical peripartum period.

888 Side Effects and Treatment Adherence After ART Initiation in Pregnancy in South Africa

Tamsin Phillips[1]; Allison V. Zerbe[2]; Agnes Ronan[1]; Claude A. Mellins[3]; Robert H. Remien[3]; James A. McIntyre[4]; Greg Petro[1]; Elaine J. Abrams[2]; Landon Myer[1]

[1]University of Cape Town, Cape Town, South Africa; [2]ICAP at Columbia University, New York, NY, US; [3]New York State Psychiatric Institute and Columbia University, New York, NY, US; [4]Anova Health Institute, Johannesburg, South Africa

Background: Recent guideline changes call for use of triple-drug antiretroviral therapy (ART) in all HIV-infected pregnant women in South Africa. However there have been few studies on side effects (SE) after ART initiation in pregnancy and their impact on ART adherence.

Methods: Consecutive pregnant women seeking antenatal care (ANC) in Gugulethu, Cape Town were recruited at first ANC visit. Women initiated a once-daily fixed-dose combination of TDF300mg+FTC300mg+EFV600mg and attended scheduled assessments throughout the antenatal period to delivery. Structured questionnaires assessed self-reported SE, based on Division of AIDS categories, and missed ART doses in the preceding 30 days. The frequencies of different classes of SE were examined; multiple logistic regression was used to investigate adjusted associations between SE and non-adherence during the first two months on ART.

Results: From April 2013–May 2014, 471 women were enrolled (median age, 28 years; median nadir CD4 cell count, 343 cells/μL; median gestational age, 21 weeks). During the first two months on ART 92% of women reported at least one SE and 14% reported at least one missed dose (Table 1). Central nervous system (CNS) SE (dizziness, unusual dreams, headaches) were most commonly reported (73% of women), followed by gastrointestinal tract (GIT) SE (66%), and skin SE (predominantly rash, 19%); in addition, 63% reported non-specific systemic SE (fatigue, fever, generalised pain). Self-report of missing any ART during the preceding 30 days was more common in women who reported any skin or GIT SE (p=0.008 and 0.031, respectively) but non-adherence was not associated with CNS or systemic SE. After adjusting for age and duration of ART use, women's reporting of skin SE remained associated with non-adherence (odds ratio [OR], 2.33; 95% confidence interval [CI], 1.27-4.27) but GIT SE was only weakly associated with non-adherence (OR 1.79, 95% CI, 0.94-3.40).

Table 1: Reported side effects (SE) following ART initiation during pregnancy in Cape Town, South Africa, with associations with 30-day treatment adherence. Note participants could report >1 SE.

All cells are N (%)	**All women**	**Number of missed doses in previous 30 days**				**p-value** (any vs none)
		None	*1-2*	*3 or more*	*Any missed*	
Number of women	**471**	**407 (86)**	**43(9)**	**21(5)**	**64(14)**	
Any side effect reported	**432(92)**	**371(91)**	**41(95)**	**20(95)**	**61(95)**	**0.335**
Number of SE classes reported						
None	*39(8)*	*36(9)*	*2(5)*	*1(5)*	*3(5)*	**0.015**
1 only	*89(19)*	*79(19)*	*8(17)*	*2(10)*	*10(16)*	
2	*93(20)*	*85(21)*	*4(9)*	*4(19)*	*8(13)*	
3	*209(44)*	*178(44)*	*21(49)*	*10(48)*	*31(48)*	
4	*41(9)*	*29(7)*	*8(19)*	*4(19)*	*12(19)*	
Any GIT SE	**312(66)**	**262(64)**	**31(72)**	**19(90)**	**50(78)**	**0.031**
Nausea	*222(47)*	*190(47)*	*21(49)*	*11(52)*	*32(50)*	
Vomiting	*114(24)*	*96(24)*	*12(28)*	*6(29)*	*18(28)*	
Diarrhoea	*128(27)*	*103(26)*	*17(40)*	*8(38)*	*25(39)*	
Appetite change	*147(31)*	*120(29)*	*17(40)*	*10(48)*	*27(42)*	
Other GIT	*3(1)*	*3(1)*	*0*	*0*	*0*	
Any CNS SE	**346(73)**	**296(73)**	**33(77)**	**17(81)**	**50(78)**	**0.363**
Dizziness	*243(52)*	*203(50)*	*25(58)*	*15(71)*	*40(63)*	
Unusual dreaming	*159(34)*	*139(34)*	*13(30)*	*7(33)*	*20(31)*	
Headache	*178(38)*	*152(37)*	*17(40)*	*9(43)*	*26(41)*	
Insomnia	*7(1)*	*6(1)*	*1(2)*	*0*	*1(2)*	
Other CNS SE	*1(<1)*	*0*	*0*	*1(5)*	*1(2)*	
Any skin SE	**90(19)**	**70(17)**	**15(35)**	**5(24)**	**20(31)**	**0.008**
Rash	*87(18)*	*68(17)*	*15(35)*	*4(19)*	*19(30)*	
Pruritus	*3(1)*	*2(<1)*	*1(2)*	*0*	*1(2)*	
Other skin	*1(<1)*	*0*	*0*	*1(5)*	*1(2)*	
Any systemic SE	**295(63)**	**250(61)**	**31(72)**	**14(67)**	**45(70)**	**0.172**
Fever	*127(27)*	*105(26)*	*14(33)*	*8(38)*	*22(34)*	
Other pain	*120(25)*	*96(24)*	*17(40)*	*7(33)*	*24(38)*	
Sweats	*92(20)*	*72(18)*	*12(28)*	*8(38)*	*20(31)*	
Fatigue	*209(44)*	*175(43)*	*23(53)*	*11(52)*	*34(53)*	
Peripheral neuropathy	*10(2)*	*9(2)*	*1(2)*	*0*	*1(2)*	
Other musculoskeletal SE	*4(1)*	*3(1)*	*1(2)*	*0*	*1(2)*	

Conclusions: These novel data show a high frequency of self-reported SE in pregnant women starting ART in a primary care setting, and suggest that specific SE may contribute to non-adherence in the first months on ART. This SE frequency is higher than reported in non-pregnant adults in South Africa and the reasons for this require additional investigation. Interventions to reduce SE (e.g. lower EFV dosing) and/or mitigate the behavioural impact of SE (e.g. counselling interventions) require particular attention in the context of pregnancy.

889 Efficacy of Mobile Phone Use on Adherence to Nevirapine Prophylaxis and Retention in Care Among HIV-Exposed Infants

Lilian M. Kebaya; Dalton Wamalwa; Nyambura Kariuki; Bashir Admani; Ruth W. Nduati

University of Nairobi, Nairobi, Kenya

Background: HIV is a major contributor to infant mortality. A significant gap remains between the uptake of infant and maternal ARV regimens and only a minority of HIV-exposed infants receives prophylaxis and safe infant feeding. Losses to follow-up of HIV-exposed infants are associated with shortcomings of facility-based PMTCT models with weak community support of linkages. Rapid expansion of mobile phone coverage in Africa, and in Kenya, presents an opportunity to strengthen linkages between caregivers and health providers. Mobile phone use offers an option to improving care and promoting retention for the mother-baby pairs, which is a major challenge in efforts to achieving an HIV-free generation.

Objectives: To compare self-reported adherence to infant nevirapine (NVP) prophylaxis and retention in care over 10 weeks in HIV exposed infants randomized to 2-weekly mobile phone calls (intervention) versus no phone calls (control).

Design: Open label Randomized controlled trial

Methods: One hundred and fifty HIV infected women drawn from 3 health facilities in Western Kenya and their infants were randomly assigned to receive either phone-based reminders on PMTCT messages or standard health care messages (no calls) within 24 hours of delivery. The group in the intervention arm received phone calls fortnightly. At 6 and 10 weeks following randomization we collected data on infant adherence to nevirapine, mode of infant feeding, early HIV testing and retention in care in both study arms. All analyses were intention to treat.

Results: Seventy five women were each randomized to the intervention and control arms respectively. At 6 weeks follow-up 68 (90.7%) participants in the intervention arm reported adherence to infant NVP prophylaxis, compared with 54 (72%) participants in the control group ($p = 0.005$). Participants in the intervention arm were also significantly more likely to be retained in care than those in the control group. At 6 weeks 59 mother-infant pairs (78.7%) attended scheduled visits with the visits coinciding with the appointment date versus 44 (58.7%) in the control arm ($p = 0.009$). At 10 weeks the revisit rates were 69.3% (52) in intervention arm and 37.3% (28) in control arm for the 150 mother-infant pairs evaluated ($p < 0.001$).

Conclusions: These results suggest that phone calls can be an important tool to improve adherence to infant NVP prophylaxis and retention in care for HIV-exposed infants.

890 HIV Care Continuum for Postpartum Women in Philadelphia: Barriers and Facilitators

Joella W. Adams[1]; Kathleen Brady[1]; Yvonne Michael[3]; Baligh R. Yehia[4]; Florence Momplaisir[2]

[1]Philadelphia Department of Public Health, Philadelphia, PA, US; [2]Drexel University College of Medicine, Philadelphia, PA, US; [3]Drexel University School of Public Health, Philadelphia, PA, US; [4]University of Pennsylvania, Philadelphia, PA, US

Background: There are 280,000 women with HIV in the U.S. and the number of HIV-infected women giving birth increased 30% from 2001-2010. HIV-infected women are at risk of virologic failure postpartum. We evaluated factors influencing HIV outcomes in postpartum HIV-infected women.

Methods: Using 2005-2011 surveillance data, we conducted a retrospective cohort study of 733 deliveries from 591 HIV-infected women in Philadelphia. Outcomes of interest included retention in care at 1 and 2 years postpartum (≥1 CD4 or viral load (VL) in each 6 month interval of the 12 or 24 month period with ≥90 days between tests) and viral suppression at 1 and 2 years postpartum (VL <200 copies/ml at the last measure of the 12 or 24 month period). Multivariate logistic regression models evaluated factors associated with the last two steps of the care continuum. Predictors of interest included early postpartum care engagement (≥1 CD4 or VL within 90 days of delivery), timing of HIV diagnosis (made ≥2 years, <2 years, or during pregnancy), viral suppression at delivery, previous pregnancy with HIV and quality of prenatal care evaluated with the Kessner Index, a validated measure taking into account the trimester of entry into care, week of gestational delivery, and number of prenatal visits.

Results: Of 733 deliveries, 43% engaged in care within 90 days postpartum, 46% and 30% were retained in care and virally suppressed at year one, and 25% and 32% were retained in care and virally suppressed at year two. Retention in care and viral suppression significantly improved over time (p<.0001). Timing of HIV diagnosis and early postpartum engagement were the only 2 variables associated with both retention and viral suppression (Table1). Women diagnosed with HIV during pregnancy were half as likely to be retained at year one and two postpartum (AOR 0.53, 95% CI 0.32-0.88; AOR 0.50, 95% CI 0.29-0.88) and half as likely to suppressed at year two postpartum (AOR 0.51, 95% CI 0.32-0.83). Women with early postpartum care engagement were more likely to be retained (AOR, 7.7, 95% CI: 5.3-11.2) and virally suppressed (AOR, 1.9, CI: 1.3-2.7) at year one postpartum. Early engagement was associated with retention (AOR, 4.8, CI: 3.2-7.2) but not viral suppression at year two postpartum.

Table I. Factors associated with two or more steps in the HIV care continuum of HIV-infected women one and two years postpartum (n=733), Philadelphia, Enhanced Perinatal Surveillance and HIV/AIDS Reporting Systems.

	Retention in Care at One Year		Viral Suppression at One Year		Retention in Care at Two Years		Viral Suppression at Two Years	
	AOR	95%(CI)	AOR	95%(CI)	AOR	95%(CI)	AOR	95%(CI)
ART Guideline Time Period								
<200 (2005-2006)	**1**	n/a	**1**	n/a	**1**	n/a	**1**	n/a
<350 (2007-2008)	**1.30**	0.84-2.01	**2.69**	1.66-4.39	**2.27**	1.35-3.81	**1.66**	1.07-2.56
<500 (2009-2011)	**2.54**	1.55-4.12	**4.45**	2.62-7.56	**2.81**	1.59-4.97	**2.66**	1.65-4.29
Previous Pregnancy with HIV (Yes vs. No)	**0.97**	0.62-1.52	**0.73**	0.48-1.11	**0.94**	0.60-1.46	**0.57**	0.39-0.85
Adequacy of Prenatal Care (Kessner)								
Adequate	**1**	n/a	**1**	n/a	**1**	n/a	**1**	n/a
Intermediate	**0.66**	0.43-1.00	**0.68**	0.44-1.03	**0.63**	0.40-0.98	**0.82**	0.55-1.21
Inadequate/no prenatal care	**0.68**	0.43-1.08	**0.67**	0.41-1.09	**0.38**	0.23-0.64	**0.75**	0.49-1.16
Timing of HIV Diagnosis								
≥ 2 yr before delivery	**1**	n/a	**1**	n/a	**1**	n/a	**1**	n/a
< 2 yr before delivery	**0.63**	0.38-1.04	**0.74**	0.44-1.25	**0.71**	0.40-1.24	**0.82**	0.51-1.33
During pregnancy	**0.53**	0.32-0.88	**0.96**	0.58-1.59	**0.50**	0.29-0.88	**0.51**	0.32-0.83
VL Undetectable Before Delivery (Yes vs. No)	**1.04**	0.72 -1.50	**2.34**	1.59-3.44	**1.13**	0.76-1.68	**2.21**	1.55-3.15
Early Postpartum Care Engagement (Yes vs. No)	**7.70**	5.29-11.2	**1.87**	1.29-2.69	**4.82**	3.23-7.19	**0.97**	0.69-1.38

* Multivariate models include age group and race/ethnicity as covariates

Conclusions: Postpartum HIV-infected women have low rates of retention in care and viral suppression. Interventions aiming at early HIV diagnosis and engaging women in care after delivery have the potential to improve long term clinical outcomes.

TUESDAY, FEBRUARY 24, 2015

Session P-T7 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Pharmacokinetics and Safety of ART During Pregnancy

891 Raltegravir Plasma Concentrations on HIV-1 Infected Pregnant Women

Emilie Belissa; Amine Benchikh; Charlotte Charpentier; Morgane Valentin; Agnes Bourgeois-Moine; Sylvie Lariven; Florence Damond; Yazdan Yazdanpanah; Sophie Matheron; **Gilles Peytavin**

APHP, Bichat-Claude Bernard Hospital, Paris, France

Background: Raltegravir (RAL) is used in association with other antiretrovirals (ARV) in pregnant women as a formal tritherapy or an additional ARV as intensification in late presenters or in low level viremia. Because of physiological changes during pregnancy, RAL plasma concentration 12 hours post-dose (C12h) at different trimester of pregnancy is important to evaluate. Secondary objectives are assessment of efficacy and safety of RAL containing regimen during pregnancy

Methods: single center, observational, descriptive study. The main inclusion criteria were pregnant women treated with RAL 400mg BID containing regimen with available demographic, immuno-virological and therapeutic data. ARV maternal plasma and cord blood concentrations were performed using UPLC-MS/MS. All results were expressed as median [IQR25-75%] and Mann-Whitney test was used

Results: among the 23 women enrolled (31 yrs, 19 African), 11 of them received RAL as intensification of ongoing ARV treatment. Their characteristics were: duration of HIV infection 8.3 yrs (4.0-12.1); Plasma HIV-RNA (pVL) before ARV 32,365 c/mL (3,792-200,500), before RAL 544 c/mL (156-13,232) and before pregnancy 184 c/mL (35-17,650); Nadir CD4 224/mm^3 (42-352) and CD4 before pregnancy 434/mm^3 (280-529), duration of ARV 7.1 yrs (1.1-11.7); duration of RAL 8.1 months (2.6-67.1). All patients received RAL+PI/r+NRTIs except one (RAL+ABC/3TC). PI/r were: DRV/r (17), LPV/r (4) and SQV/r (1). RAL C12h at 2nd and 3rd trimesters was 84ng/mL (32-215, n=20) and 58ng/mL (20-185, n=47) (p=0.52), respectively. Cord blood/maternal plasma concentrations ratio ($R_{CB/MP}$) was 1.03 (0.50-1.43, n=4). The mode of delivery was available in 16 women (10 caesarians). At delivery, 18 of 23 patients had pVL<50c/mL and all pVL<400c/mL. Among the 5 women with detectable pVL, 2 was non adherent and 3 late presenters. Neonate characteristics were: gestational age 38.7 weeks (38.1-40.1; n=20), Hb 16,4 g/dL (15,1-17.9; n=9), bilirubinemia 30 µmol/L (21-36; n=7). No neonate was HIV infected. No adverse event was observed in mothers and neonates during the follow-up

Conclusions: RAL plasma concentrations are not modified during pregnancy and are similar with historical data in non pregnant population. Besides, RAL containing regimen seems to be efficient and safe for mother and her children, probably due to a favorable placental transfer ($R_{CB/MP}$ >1.0)

892 Etravirine Pharmacokinetics During Pregnancy and Postpartum

Brookie M. Best[1]; Angela Colbers[2]; Jiajia Wang[3]; Graham Taylor[4]; Alice Stek[5]; Marjo van Kasteren[6]; Mark Mirochnick[7]; David Burger[2]

On behalf of the IMPAACT P1026s Protocol Team and the PANNA Network

[1]University of California San Diego, San Diego, CA, US; [2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; [3]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, US; [4]Imperial College Healthcare NHS Trust, London, United Kingdom; [5]University of Southern California School of Medicine, Los Angeles, CA, US; [6]St. Elisabeth Hospital, Tilburg, Netherlands; [7]Boston University School of Medicine, Boston, MA, US

Background: Maintaining therapeutic concentrations of antiretrovirals (ARVs) throughout pregnancy is critical to prevent perinatal transmission and maternal resistance development. Physiological changes during pregnancy may alter the pharmacokinetics (PK) of prescribed medicines, particularly those metabolized by cytochrome (CYP) P450 enzymes. To date, no studies have reported etravirine (ETV) PK during pregnancy. ETV is metabolized by and inhibits or induces CYP 3A4, 2C9 and 2C19. The goal was to determine ETV PK parameters during the 2nd and 3rd trimesters compared to the same subjects postpartum and to historical non-pregnant controls.

Methods: P1026s is an ongoing, multi-center, multi-arm, prospective PK study of HIV-1 infected pregnant women on ARVs for routine care. This arm enrolled women on ETV 200 mg twice daily. The PANNA Study is a similar design, enrolling in European countries. Steady-state 12-hour ETV profiles were obtained in the 2nd and 3rd trimesters, and at 4-12 weeks postpartum. Maternal and cord blood samples were collected at delivery. The P1026s target steady-state ETV 12-hour AUC was 2.5 µg*hr/mL (10th percentile in non-pregnant historical controls). The 50th percentile AUC in non-pregnant controls is 4.2 µg*hr/mL, and a suggested minimum concentration from the GRACE trial is 0.16 mg/L. Paired PK parameters were compared with the Wilcoxon signed-rank test at a significance of p<0.05.

Results: Five, 12 and 8 women completed 2nd trimester, 3rd trimester, and postpartum PK evaluations. Median (range) age was 26 (19-43) years. Seven patients were black; 6 Hispanic; and 1 Caucasian. At delivery 9/10 patients had an HIV viral load <50 copies/mL. One subject took ETV 400 mg once daily; her oral clearance (CL/F), AUC_{0-12}, and half-life values are included in the summary data, while individual concentrations were excluded. ETV PK parameters are presented below. The median (range) ratio of cord blood/maternal plasma concentrations (n=5) was 0.59 (0.19-4.25). Six children were HIV uninfected; for five children results are pending.

Parameter	2nd trimester: [a] (n=5)	3rd Trimester: [a] (n=12)	Postpartum: [a] (n=8)	3rd Trimester/ Postpartum[b] (n=8)
AUC_{0-12}, µg h/mL	4.5 (3.4 – 10.7)	8.3* (2.7 – 31.0)	5.3 (2.1 – 16.4)	1.40 (1.05 – 1.75)
Cl/F, L/h	44.4 (18.7 – 58.8)	24.4* (6.5 – 74.1)	38 (12.2 – 95.2)	0.88 (0.81 – 0.95)
Vd/F, L	1439 (337 – 27,878)	520 (154 – 3563)	824 (225 – 1758)	0.95 (0.87 – 1.04)
C_{max}, µg/mL	0.70 (0.44 – 1.05)	1.02* (0.26 – 3.47)	0.63 (0.30 – 1.60)	1.09 (1.05 – 1.14)
T_{max}, hr	2 (0 – 8)	3.5 (2 – 6)	4 (1 – 4)	-
C_0, µg/mL	0.26 (0.07 – 1.05)	0.60 (< 0.005 – 2.64)	0.38 (<0.005 – 1.21)	1.92 (0.74 – 3.11)
C_{12}, µg/mL	0.36 (0.08 – 0.75)	0.48* (0.08 – 1.94)	0.33 (0.07 – 1.14)	1.14 (1.05 – 1.23)
$T_{1/2}$	45.2 (5.3 – 434.7)	12.5 (6.2 – 81.5)	26.4 (4.8 – 36.5)	1.12 (0.87 – 1.37)
≥ AUC Target	5/5 (100%)	12/12 (100%)	7/8 (88%)	-
≥ C_{12} Target	4/5 (80%)	11/12 (92%)	6/8 (75%)	-

[a] Reported as Median (Range) or Number (Percent)
[b] Reported as Geometric Mean Ratio (90% Confidence Intervals)
* p < 0.05 compared to postpartum

Conclusions: While 2nd trimester and postpartum ETV PK were similar to non-pregnant adult PK, 3rd trimester exposure was significantly higher than postpartum and historical controls. The metabolism of ETV is complex; pregnancy, ETV itself and other drugs alter the activity of these pathways. The increased 3rd trimester exposure may be due to decreases in CYP2C19 activity and ritonavir exposure. No ETV dose change is needed during pregnancy.

893 Pharmacokinetics of Etravirine in HIV-1–Infected Pregnant Women

M Ramgopal[1]; O Osiyemi[2]; C Zorrilla[3]; HM Crauwels[4]; R Ryan[5]; K Brown[6]; V Hillewaert[7]; B Baugh[6]

[1]Midway Immunology and Research Center, Fort Pierce, FL, US; [2]Triple O Research Institute PA, West Palm Beach, FL, US; [3]University of Puerto Rico School of Medicine, San Juan, US; [4]Janssen Infectious Diseases, Beerse, Belgium; [5]Janssen Research & Development, Titusville, NJ, US; [6]Janssen Therapeutics, Titusville, NJ, US; [7]Janssen Research & Development, Beerse, Belgium

Background: Antiretroviral (ARV) therapy during pregnancy has dramatically reduced the risk of mother-to-child transmission. Physiologic changes during pregnancy can affect the PK of ARVs.

Methods: Phase IIIb study evaluating HIV-1–infected pregnant women (age ≥18 years), in the 2nd trimester of pregnancy, receiving ETR 200mg bid with other ARVs. ETR plasma concentrations were assessed predose and 1, 2, 3, 4, 6, 9 and 12 hours postdose during the 2nd and 3rd trimesters and (6-12 weeks) postpartum. ETR PK parameters were derived using non-compartmental analysis. Safety and efficacy were investigated at each visit and summarized using descriptive statistics.

Results: Fifteen women (11 black, 2 Hispanic, 2 white) were enrolled; 13 had evaluable PK. ETR AUC_{24h}, C_{min} and C_{max} were higher by 46% (LS Means ratio, 90% CI: 1.46, 1.12-1.90), 131% (2.31, 1.26-4.22) and 39% (1.39, 1.15-1.67) during the 2nd trimester and by 28% (1.28, 0.98-1.69), 93% (1.93, 1.03-3.61) and 31% (1.31, 1.08-1.59) during the 3rd trimester, versus postpartum. ETR post-partum PK was comparable to historic controls in HIV-1 infected subjects (DUET). Though mean ETR exposures during pregnancy were higher compared to post-partum, the observed exposures were still in range with those previously observed in HIV-1 infected subjects treated with ETR 200 mg bid. Unbound ETR PK will be explored. Median baseline (BL) viral load (VL) was 49 copies/mL; for one woman, BL VL was 54,000 copies/mL and remained detectable throughout the study. All other women had VL<400 copies/mL during pregnancy (>90% had VL<50 copies/mL). The median increases in CD4 from baseline were 29 and 45 cells/mm^3 for the 2nd and 3rd trimester respectively, and were >100 cells/mm^3 postpartum. Four subjects had serious adverse events (SAEs), none of which were at least possibly related to ETR (premature rupture of membranes; hypertension; headache; and one subject had 3 SAEs: pregnancy induced hypertension [twice] and premature labor). One subject had a treatment emergent adverse event (atopic dermatitis) that was at least possibly related to study drug. All infants were HIV-negative.

Conclusions: ETR exposure increased during pregnancy; this was not associated with an increased occurrence of SAEs. The regimen was well tolerated. Virologic response was maintained throughout the study and there was no mother-to-child transmission. These data indicate ETR 200 mg bid could be a treatment option for HIV-1 infected pregnant women.

894 Pharmacokinetics of Rilpivirine in HIV-Infected Women During Pregnancy and Postpartum

Mark Mirochnick[1]; Brookie M. Best[2]; Alice Stek[3]; Regis Kreitchmann[8]; Jiajia Wang[4]; David Shapiro[4]; Elizabeth Smith[5]; Lynne Mofenson[6]; Tim R. Cressey[7]; Edmund Capparelli[2]

[1]Boston University School of Medicine, Hingham, MA, US; [2]University of California San Diego, San Diego, CA, US; [3]University of Southern California, Los Angeles, CA, US; [4]Harvard School of Public Health, Boston, MA, US; [5]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US; [6]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US; [7]Harvard School of Public Health/Chiang Mai University, Chang Mai, Thailand; [8]Irmandade da Santa Casa de Misericordia de Porto Alegre, Porte Alegre, Brazil

Background: Rilpivirine (RPV), a 2nd generation non-nucleoside reverse transcriptase inhibitor, has increased absorption when taken with food and is primarily metabolized by cytochrome P450 3A4. During pregnancy, physiological changes including alterations in intestinal transit time and increased CYP 3A4 activity may impact systemic drug exposure. The impact of pregnancy on RPV pharmacokinetics (PK) is unknown.

Methods: IMPAACT Protocol P1026s is an ongoing, multicenter, non-blinded prospective study evaluating the PK of antiretrovirals (ARV) in pregnant HIV-infected women that included a cohort of US pregnant women receiving as part of clinical care combination ARV regimens including RPV 25 mg once daily with food. Intensive steady-state 24 hour PK profiles were performed during the 2nd trimester, 3rd trimester and 6-12 weeks postpartum. Maternal and umbilical cord blood samples were obtained at delivery. Plasma RPV concentrations were measured using liquid chromatography-mass spectrometry, with a lower limit of quantitation of 0.010 mcg/mL. The minimum target for RPV AUC_{24} was 0.88 mcg*hr/mL, the 10th percentile AUC for non-pregnant adults. Pairwise comparisons within each subject between time points were performed using a two-sided Wilcoxon signed rank test.

Results: RPV PK data were available for 26 women. PK parameters are presented in the table below as median (range). There were no significant differences in any PK parameters for the 2nd or 3rd trimester compared to postpartum. Mean (90% CI) for the ratio of 2nd or 3rd trimester to postpartum log-transformed pk parameters were 1.05 (0.78-1.32) and 1.01 (0.77-1.24) for AUC and 0.94 (0.69-1.18) and 0.91 (0.70-1.12) for C(24)h, respectively. Median (range) RPV concentrations (mcg/mL) in cord blood and maternal delivery samples, and their ratio were 0.054 (BQL (below quantitation limit) - 0.102), 0.103 (BQL – 0.234) and 0.53 (0.38 – 0.83). RPV was well tolerated by all study mothers. Viral load at delivery was below 400 copies/mL for 22 of 24 women and below 50 copies/mL for 17 of 24. No infants were HIV infected, but infection data through the final 24 week visit are only available for 7 infants.

	2nd trimester (n=16)	3rd trimester (n=26)	Postpartum (n=16)
AUC (mcg*hr/mL)	2.18 (0.87-12.40)	1.99 (0.56-4.31)	2.58 (0.19-6.74)
Met AUC target/total (%)	13/14 (92.8%)	22/24 (91.7%)	15/16 (93.8%)
C(24)h (mcg/mL)	0.070 (0.037-0.517)	0.061 (BQL-0.181)	0.098 (BQL-0.299)
CL/F (L/hr)	11.6 (2.0-28.8)	12.6 (5.8-45.0)	9.7 (3.7-132.9)

RPV PK Parameters

Conclusions: No significant differences in RPV exposure during pregnancy and postpartum were observed. The standard RPV dose provides adequate RPV exposure during pregnancy.

894-A Pharmacokinetics of Rifampin in TB/HIV-Coinfected Women: Does Pregnancy Matter?

Paolo Denti[1], Helen McIlleron[1], Neil Martinson[2], Silvia Cohn[2], Jennifer Hoffmann[2], Richard Chaisson[2], Kelly Dooley[2], Fildah Mashabela[3], Regina Msandiwa[3]
On behalf of the TSHEPISO Study Team

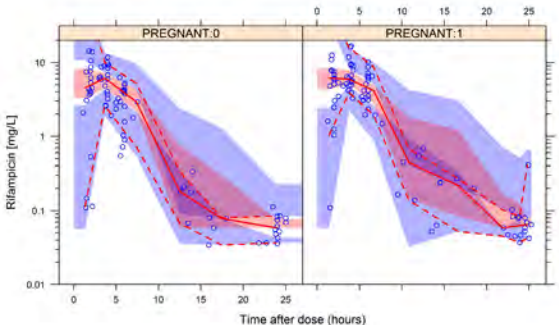
[1]*Division of Clinical Pharmacology, University of Cape Town, Cape Town, South Africa;* [2]*Johns Hopkins University School of Medicine, Baltimore, Maryland, United States;* [3]*Perinatal HIV Research Unit, University of the Witwatersrand, Soweto, South Africa*

Background: Pregnant women are at high risk of progression from latent to active TB. They are typically treated with the same regimen as non-pregnant adults. Pregnancy, though, induces physiological changes that impact drug exposures. The effects of pregnancy on the pharmacokinetics (PK) of rifampin, the key sterilizing drug in anti-TB treatment, are unknown.

Methods: Prospective cohort of pregnant, HIV-infected women with tuberculosis in Soweto, South Africa. Women taking standard first-line TB treatment had PK sampling at around 37 weeks' gestation or delivery, then at around 6 weeks postpartum. Blood samples were generally collected pre-dose, then 2, 4, and 6-8 hours post-dose. Cord blood was also collected. Rifampin was quantified using LC-MS/MS, with lower limit of quantification 0.117 mg/L. A population PK model was developed using nonlinear mixed-effects modeling. Treatment outcomes and transmission events were collected.

Results: PK information was available from 33 pregnant women with HIV receiving standard TB treatment, median age and weight were 29 years and 64 kg, respectively. A population PK analysis using 48 PK profiles and 183 samples was performed. A one-compartment model with first-order elimination and transit compartment absorption described the data well. Allometric scaling based on total body weight was applied to clearance and volume. Pregnancy reduced rifampin clearance by 14% ($p<0.026$). No other covariates influenced PK. Based on individual post-hoc estimates, median (IQR) rifampin AUC0-24h and Cmax during pregnancy were 40.8 mg.h/L (27.1-54.2) and 8.4 mg/L (7.1-10.0), compared to 37.4 (26.8-50.3) and 9.0 (6.6-11.9) post-partum. Of the twenty-two available cord blood samples, rifampicin was detectable (>0.117 mg/L) in eight samples. Cord blood concentrations were generally lower than maternal peri-partum concentrations (when available) and detectable only if delivery occurred within 8 hours after maternal dose intake.

Conclusions: Rifampin exposures were increased modestly during the last trimester of pregnancy, seemingly due to decreased clearance. This suggests that no dose adjustment is necessary in pregnancy. Rifampin was detected in cord blood samples. The clinical relevance of exposures to this potent inducer of metabolizing enzymes among HIV-exposed infants is unclear.



Prediction-corrected visual predictive check of the final model, stratified by pregnancy status. The solid and dashed lines are the 5th, 50th, and 95th percentiles of the observed data, while the shaded areas represent the 95% confidence intervals for the same percentiles as predicted by the model. An appropriate model is expected to have all observed percentiles within the simulated confidence intervals.

TUESDAY, FEBRUARY 24, 2015

Session P-T8 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Planning and Preventing Pregnancy

895 Safer Conception Delayed by Lack of HIV Viral Suppression

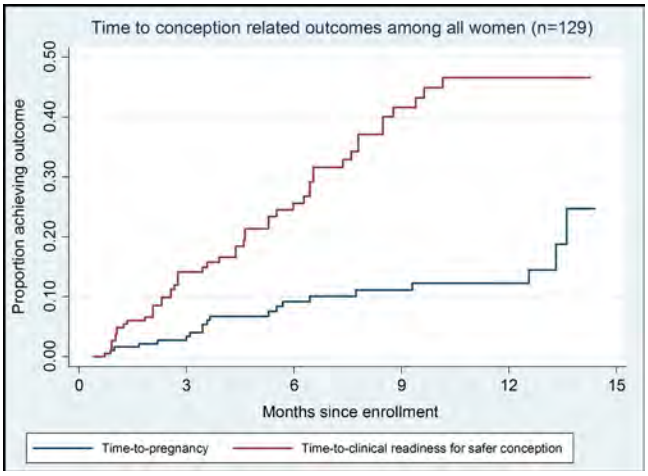
Sheree R. Schwartz[1]; Rebecca Phofa[2]; Nompumelelo Yende[2]; Jean Bassett[2]; Nora West[2]; Ian Sanne[3]; Annelies Van Rie[1]

[1]*University of North Carolina, Chapel Hill, NC, US;* [2]*Witkoppen Health and Welfare Centre, Johannesburg, South Africa;* [3]*University of the Witwatersrand, Johannesburg, South Africa*

Background: Safer conception strategies can reduce transmission risks among couples and infants when one or both partners are HIV-infected. Data on safer conception from Sub-Saharan Africa are not available. We report outcomes from a safer conception clinic in South Africa.

Methods: From July 2013-September 2014, 129 women and 70 men enrolled in *Sakh'umndeni*, a safer conception clinic at the primary care Witkoppen Health and Welfare Centre in Johannesburg. Services offered are antiretroviral therapy (ART) independent of CD4 count, pre-exposure prophylaxis, education on importance of viral load suppression, timed unprotected sex, and self-insemination when the male partner is HIV-uninfected. We estimate time-to-clinical readiness to safely conceive (TTRC), time-to-pregnancy (TTP), and describe viral suppression at pregnancy diagnosis. TTCR is defined as time from enrollment to viral suppression in both partners, HIV negative status confirmation in serodiscordant partner, and absence of contraindications for safe conception.

Results: At enrollment, most women (122/129, 95%) were HIV-infected, of which 85% (104/122) were on ART, and 48% (59/122) virally suppressed. While encouraged to attend as a couples, only 54% (70/129) of male partners ever attended. At presentation 67% of men were HIV-infected, 74% (35/47) were on ART and 19% (9/47) were virally suppressed. To date, less than half of 129 women achieved clinical readiness to safely conceive (Figure 1). Common reasons for not being ready were lack of viral suppression (63.5%) and awaiting partner clinic attendance (17.6%). Median TTCR among the 36 women ever ready to safely attempt conception was 3.2 months [IQR 1.3-6.2] and 17% (6/36) became pregnant. While only 9% of couples were clinically ready to conceive by 6 months of follow-up, 26% of women had conceived by then (Figure 1). We observed 20 pregnancies, 17 among HIV positive women. All women safely conceiving were virally suppressed at pregnancy diagnosis (n=4) or had repeat HIV-negative test results (n=2). All (4/17) HIV positive women not virally suppressed at pregnancy diagnosis had viral loads <1000. No partner or infant infections have been observed.



Conclusions: Male partner participation and achieving viral suppression are major barriers to safe conception. Even though many couples do not wait to conceive until both partners were virally suppressed, use of safer conception strategies reduced risks by lowering viral load and limiting unprotected sex among those conceiving prematurely.

896 Preventing Unintended Pregnancy and HIV: The HIV Treatment Cascade and Contraceptive Choices

Julia Raifman[1]; Terusha Chetty[2]; Frank Tanser[2]; Tinofa Mutevedzi[2]; Philippa Matthews[2]; Kobus Herbst[2]; Deenan Pillay[2]; Till Barnighausen[1]

[1]Harvard School of Public Health, Washington, DC, US; [2]Africa Centre for Health and Population Studies, Mtubatuba, South Africa

Background: Contraception using condoms is recommended for women living with HIV because it prevents unintended pregnancy, acquisition of other sexually transmitted diseases, and onward transmission of HIV. Dual-method dual protection contraception (condoms with other methods) has greater contraceptive effectiveness than single-method dual protection contraception (condoms alone) and is also preferable to single protection (non-condom methods), which only protect against unintended pregnancy without preventing HIV and other STI transmission. We estimate the effect of progression along the HIV treatment cascade on contraceptive use and choice among HIV-infected women in a high prevalence rural South African setting.

Methods: We linked population-based surveillance data on contraception collected by the Wellcome Trust-funded Africa Centre for Health and Population Studies to data from the local antiretroviral treatment (ART) program in Hlabisa sub-district, KwaZulu-Natal. We estimated a bivariate probit model of the effects of progressing through the cascade on contraceptive choice among HIV-infected, sexually active women aged 15-49 years (N=3169), controlling for potential confounders based on individual and household characteristics.

Results: Overall contraception use increased across the cascade from <40% among HIV-infected women who did not know their status to >70% among women on ART for 4-7 years. Table 1 shows the average marginal effects of movement through the treatment cascade on contraceptive choice. We found that becoming aware of HIV-positive status increased the probability of women using single-method dual protection by 4.6 percentage points (pp, p=0.030) and the probability of using dual-method dual protection by 3.5 pp (p=0.001) relative to women who were unaware of their HIV-positive status. Being on ART for less than a year increased the probability of using single-method dual protection by 10.3 pp (p=0.003) and the probability of dual-method dual protection by 5.2 pp (p=0.007), while being on ART for 4-7 years increased the probability of using single-method dual protection by 21.6 pp (p<0.001) and dual-method dual protection by 11.2 pp (p<0.001).

Table 1: Effects of progression through the HIV treatment cascade on contraception: Average marginal effects

	No contraception			Single protection			Single-method dual protection			Dual-method dual protection		
	AME (in pp)	95% CI	p-value	AME (in pp)	95% CI	p-value	AME (in pp)	95% CI	p-value	AME (in pp)	95% CI	p-value
Stages in the HIV treatment cascade												
HIV+, unaware of HIV status	Ref			Ref			Ref			Ref		
HIV+ awareness unknown	-0.078	(-0.206 - 0.049)	0.228	-0.064	(-0.164 - 0.036)	0.207	0.121	(-0.005 - 0.246)	0.059	0.022	(-0.042 - 0.086)	0.498
HIV+, aware of HIV status	-0.094	(-0.140 - -0.047)	<0.001	0.012	(-0.028 - 0.052)	0.558	0.046	(0.005 - 0.088)	0.030	0.035	(0.014 - 0.056)	0.001
Pre-ART	-0.070	(-0.122 - -0.019)	0.008	0.025	(-0.020 - 0.070)	0.273	0.019	(-0.028 - 0.065)	0.431	0.027	(0.004 - 0.049)	0.021
0-1 years on ART	-0.129	(-0.195 - -0.063)	<0.001	-0.026	(-0.081 - 0.029)	0.352	0.103	(0.034 - 0.172)	0.003	0.052	(0.014 - 0.089)	0.007
1-2 years on ART	-0.156	(-0.225 - -0.086)	<0.001	0.006	(-0.057 - 0.069)	0.858	0.079	(0.006 - 0.152)	0.034	0.071	(0.027 - 0.115)	0.002
2-4 years on ART	-0.212	(-0.273 - -0.151)	<0.001	-0.088	(-0.134 - -0.043)	<0.001	0.222	(0.150 - 0.294)	<0.001	0.078	(0.037 - 0.120)	<0.001
4-7 years on ART	-0.249	(-0.318 - -0.180)	<0.001	-0.079	(-0.136 - -0.021)	0.007	0.216	(0.126 - 0.306)	<0.001	0.112	(0.053 - 0.171)	<0.001

Notes: The AMEs represent the change in the probability, expressed in percentage points (pp), of having the outcome when a certain stage of the cascade is reached as compared to being unaware of HIV-positive status. We controlled for age, age squared, distance to primary and secondary roads, pregnancy, parity, wealth quintile, educational attainment, self-perceived health status, marital/conjugal status, and calendar year. AME = average marginal effects, pp = percentage points, CI = confidence interval, Ref = reference category, ART = antiretroviral treatment, HIV+ = HIV-infected

Conclusions: We conclude that progression along the HIV treatment cascade significantly increased the likelihood of contraception in general and contraception with condoms in particular. HIV counseling and treatment programs are likely to contribute to HIV prevention through the behavioral pathway of changing contraception use and choice.

THURSDAY, FEBRUARY 26, 2015

Session P-T9 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Mechanisms of MTCT and Maternal/Infant Health

897 HIV Target Cells and Altered Microbiome Associated With Mixed Feeding in South Africa

Lianna F. Wood[1]; Cosette LeCiel[2]; Heather Jaspan[3]; Donald Sodora[2]

[1]University of Washington, Seattle, WA, US; [2]Seattle BioMed, Seattle, WA, US; [3]Seattle Children's Hospital, Seattle, WA, US

Background: In many South African informal settlements, 25% of new mothers are HIV-infected, and 40% of HIV-infected infants acquire HIV through breast milk. The common practice of feeding infants both breast milk and non-breast milk foods, known as mixed-feeding, increases an infant's susceptibility to HIV by up to 11 fold compared to exclusively breast feeding. We hypothesized that the increase in HIV susceptibility seen in mixed-fed infants is due to an increase in HIV target cells at the oral mucosal, the mucosal surface first encountered by HIV in breast milk, and that systemic immune activation and altered gut microbiome influence this increase in target cells.

Methods: Blood (analyzed by flow cytometry), stool (analyzed by 16S rRNA sequencing) and oral mucosa cytobrush samples (analyzed by flow cytometer, Nanostring and qPCR) were collected from 156 HIV-unexposed infants (either exclusively breast fed or mixed-fed) in Khayelitsha, South Africa at 6 and 14 weeks of age.

Results: Although at 6 weeks of age mixed and exclusively breastfed infants showed few differences in blood, oral mucosa or stool, at 14 weeks of age we observed several key differences. At 14 weeks of age, the oral mucosa of mixed-fed infants had a significantly higher percentage of HIV target cells compared to infants that were exclusively breastfed ($p=0.01$). In addition, transcript levels of 16 immune factors, including IL7R, KRT5 and CCL22, showed increased expression and 3 genes, IL18, IL12A and CASP3, showed decreased expression in the oral mucosa of mixed-fed infants. Interestingly, CCL5 (RANTES) expression was elevated in the oral mucosa of mixed-fed infants, suggesting recruitment of CCR5+ HIV target cells to the oral mucosa. In the blood, mixed fed infants also showed higher levels of activation (% HLA-DR+) in CD4+ T cells, with a specific increase in Treg (CD25hiCD39+) activation. In addition, mixed fed infants had an increased proportion of Ruminococcus in their stool microbiome.

Conclusions: These data suggest that the increased HIV susceptibility of mixed-fed infants may be mediated by an increase in HIV-susceptible cells at the first site of viral exposure, the oral mucosa, and the systemic circulation. Understanding the mechanism and the role of the gut microbiome in the increased HIV susceptibility of mixed-fed infants may inform interventions to prevent HIV transmission across mucosal surfaces.

898 Role of Type 1 IFNs in the Control of HIV-1 Infection at the Feto-Maternal Interface

Erica L. Johnson; Sahithi Boggavarapu; Elan S. Johnson; Asim A. Lal; Siddhartha Bhaumik; Murali-Krishna Kaja; Rana Chakraborty

Emory University School of Medicine, Atlanta, GA, US

Background: Low rates of *in utero* transmission of HIV-1 may reflect high endogenous placental and fetal production of type 1 interferons (IFNs). Type 1 IFNs are important for placental development, and are implicated in fetal protection against various pathogens, potentially via transcription of IFN-stimulated genes (ISGs). Type 1 IFN treatment of myeloid cells potently induces a block to HIV-1 replication at the level of viral DNA accumulation, possibly through IFN-induced host restriction factors. Although the antiviral role of IFNs is well established, it remains unclear whether placental IFNs prevent fetal viral infection *in vivo*.

Methods: With written informed consent, placentae and cord blood were collected from 15 HIV-1 and Hep. B seronegative women (>18 years) at Emory Midtown Hospital in Atlanta, GA. Peripheral blood was obtained from healthy adult volunteer donors. In this study, uninfected or HIV-1BaL-infected fetal and adult myeloid subsets were treated IFN-α or IFN-β. Viral replication was determined by HIV-1 p24 ELISA. qPCR and Western blot analysis determined the expression of ISGs and restriction factors. Transfection of SAMHD1 siRNA into myeloid subsets was performed with the N-TER Nanoparticle System. Data were analyzed by using Student's *t*-test and Mann-Whitney test.

Results: IFN-α and IFN-β potently limit HIV-1_{BaL} replication in HCs *in vitro.* In addition, these IFNs induce significant increases in expression of ISGs in fetal myeloid cells, compared to adult subset. In fetal HCs and cord blood monocytes (CBMs), treatment with IFN-α and IFN-β upregulated mRNA expression of IFN-inducible host restriction factors, APOBEC3G and Tetherin. However, SAMHD1 expression was upregulated at the mRNA level and the IFNs had no effect on protein expression. Knockdown of SAMHD1 in HC enhanced HIV-1 replication. Interestingly, the antiviral activity of type 1 IFNs was SAMHD1-indepenent.

Conclusions: The presence of type 1 IFNs at the feto-maternal interface may offset MTCT of HIV-1 through up-regulation of antiviral ISGs and interferon-inducible restriction factors with SAMHD1 having a significant role in antiviral defense. Identifying these mechanisms will provide groundbreaking information on protective correlates during repeated HIV-1 exposure and may contribute to the development of effective immunotherapies and vaccines.

899 Immune Activation During Pregnancy and Postpartum Period in Treated HIV+ Ugandans

Peter W. Hunt[1]; Helen Byakwaga[2]; Yap Boum[2]; Lynn T. Matthews[3]; Tricia H. Burdo[4]; Yong Huang[1]; Annet Kembabazi[2]; Angela Kaida[5]; David R. Bangsberg[3]; Jeffrey Martin[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Mbarara University of Science and Technology, Mbarara, Uganda; [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [4]Boston College, Boston, MA, US; [5]Simon Fraser University, Vancouver, Canada

Background: We previously observed increased maternal mortality in the postpartum period (mostly from opportunistic infections) in HIV-infected women starting ART at low CD4+ T cell counts. We sought to understand whether pregnancy-related immunologic changes might explain these findings.

Methods: We sampled HIV-infected Ugandan women starting their first ART regimen from the UARTO cohort who had live births during observation and assessed plasma markers of immune activation at 3-month intervals before, during, and in the year after pregnancy, excluding those with plasma HIV RNA levels >400 copies/ml after month 6 of ART. Pregnancy-related changes in activity of the immunoregulatory enzyme indoleamine 2,3-dioxygenase-1 (IDO, KT ratio), monocyte activation (sCD14 and sCD163), inflammation (IL-6), and coagulation (D-dimer) were assessed with linear mixed models adjusted for ART duration.

Results: Among 54 women, median pre-ART values were: age, 29 years; CD4 count, 134 cells/mm^3; plasma HIV RNA level, 5.0 $\log_{10}$ copies/ml; and 16/54 (30%) were pregnant at ART initiation. Pregnancies began at a median of 11 (IQR: -3 to 24) months after ART initiation and 7 women contributed >1 pregnancy to the analysis. During the 1st trimester of pregnancy, there was a consistent significant decline in IDO activity, monocyte activation, and IL-6 levels. In the 3rd trimester, IDO activity increased to pre-pregnancy levels while sCD14 levels remained low. In the early postpartum period, IDO activity increased 35% and remained significantly higher than pre-pregnancy baseline for 6-9 months postpartum, while other markers of monocyte activation and inflammation remained low. The coagulation marker D-dimer increased throughout pregnancy, peaking in the 3rd trimester, then steadily declined to pre-pregnancy baseline in the postpartum period.

	Mean Relative Change (95% CI) in Biomarker Compared to Non-Pregnant State*						
Plasma Biomarker	1st Trimester	2nd Trimester	3rd Trimester	<3 Months Postpartum	3-6 Months Postpartum	6-9 Months Postpartum	9-12 Months Postpartum
KT ratio	**0.90 (0.81-0.99)**	**0.88 (0.79-0.97)**	0.97 (0.86-1.11)	**1.35 (1.21-1.49)**	**1.18 (1.05-1.33)**	**1.13 (1.00-1.28)**	1.11 (0.96-1.30)
sCD14	**0.83 (0.76-0.90)**	**0.82 (0.75-0.89)**	**0.74 (0.67-0.83)**	0.93 (0.85-1.01)	**0.91 (0.84-1.00)**	**0.91 (0.83-1.00)**	**0.87 (0.77-0.98)**
sCD163	**0.84 (0.71-1.00)**	0.89 (0.75-1.05)	0.82 (0.66-1.02)	1.14 (0.96-1.36)	0.92 (0.76-1.12)	0.96 (0.78-1.17)	0.96 (0.74-1.25)
IL-6	**0.71 (0.55-0.92)**	0.81 (0.63-1.04)	0.95 (0.69-1.32)	0.98 (0.77-1.27)	**0.72 (0.54-0.94)**	0.90 (0.68-1.21)	0.79 (0.54-1.17)
D-dimer	**1.42 (1.00-2.02)**	**2.25 (1.58-3.21)**	**2.96 (1.88-4.66)**	**1.50 (1.05-2.14)**	1.27 (0.86-1.88)	1.31 (0.87-1.99)	0.93 (0.55-1.58)

*After adjustment for duration of suppressive ART modeled as linear spline (0-3, 3-6,6-12, 12-24, >24 months).

Conclusions: In treated HIV-infected women, monocyte activation and inflammation decline during pregnancy and remain low postpartum. While D-dimer increases during pregnancy, likely due to venous stasis, it declines in the postpartum period and is thus unlikely to explain postpartum mortality. Conversely, IDO activity increases significantly during the postpartum period for at least 6-9 months, potentially increasing the risk of infectious complications. These pregnancy-related immunologic changes may support earlier ART initiation in women of reproductive age and/or closer post-partum monitoring for those who start ART at low CD4+ T cell counts.

900 T-Cell Activation and Exhaustion in HIV-Infected and HIV-Uninfected Pregnant Women

Christina Fiske; Vlada Melekhin; Fernanda Maruri; Cindy Hager; Louise Barnett; Timothy Sterling; Spyros Kalams
Vanderbilt University School of Medicine, Nashville, TN, US

Background: Pregnancy alters T cell phenotype and function, but the effect of pregnancy on the immune system in the setting of HIV infection is unclear. We compared the degree of T cell activation and exhaustion and regulatory T cell (Treg) frequency in HIV-infected women pre- and postpartum.

Methods: We prospectively enrolled HIV-infected (HIV+) women on HAART and HIV-uninfected (HIV-) women and assessed immunologic parameters during the third trimester and at 24 weeks postpartum. We compared immune activation (CD38+ and HLA-DR expression), immune exhaustion of CD4+ and CD8+ cells (PD-1 expression), and Treg frequency ($CD4+CD25^{hi}CD127^{low}FoxP3+$) and function (CD39+ expression) between the two groups.

Results: We enrolled 31 HIV- and 9 HIV+ women. Twenty-seven HIV- and 7 HIV+ women had both pre- and postpartum data available for analysis. Two HIV+ women experienced postpartum viral load rebound (increase of $>0.7\log_{10}$ compared to prepartum). There was no difference in prepartum levels of CD4+ or CD8+ T cell activation between the two groups. Compared to HIV- women, HIV+ women had higher postpartum levels of CD4+CD38+HLA-DR+ (0.3%(0.2,4.4) v. 0.2%(0.1,0.3), p=0.02) and CD8+CD38+HLA-DR+ (1.6%(0.5,5.7) v. 0.5%(0.3,0.9), p=0.08) T cells. These differences were no longer statistically significant when HIV+ women with postpartum viral rebound were excluded, though the point estimates were the same. Compared to HIV- women, HIV+ women had higher postpartum expression of PD-1 on CD4+ (1.4%(1.0,2.5) vs. 0.5%(0.3,1.1), p=0.03) cells but following exclusion of HIV+ women that experienced postpartum viral rebound, this was of borderline significance (p=0.07). HIV+ women had higher levels of PD-1 on CD8+ T cells both prepartum (8.1%(8,15.4) vs. 5.1%(3.1,7.6), p=0.04) and postpartum (11.3%(10.4,15.4) vs. 5.2%(3.7,8.5), p=0.01, respectively). The postpartum CD8+PD-1+ findings were significant after excluding the HIV+ women that rebounded (p=0.03). There was no difference in pre- or postpartum Treg frequency, exhaustion, or function between the two groups.

Conclusions: We found that HIV+ women had a higher postpartum frequency of CD4+ and CD8+ T cell activation compared to HIV- women and this may have been driven in part by postpartum viral load rebound. HIV+ women had higher levels of CD8+ exhaustion markers postpartum after controlling for postpartum viral load rebound. The mechanism of decreased CD8+ exhaustion during pregnancy in HIV-infected women should be further explored.

901 HIV and Smoking Associated with Shorter Telomere Length in a Cohort of Pregnant Women

Sara Saberi[1]; Beheroze Sattha[1]; Evelyn Maan[2]; Julie Van Schalkwyk[3]; Deborah Money[1]; Hélène Côté[1]
On behalf of the CIHR Team in Cellular Aging and HIV Comorbidities in Women and Children (CARMA)
[1]University of British Columbia, Vancouver, Canada; [2]BC Women's Hospital and Health Centre, Vancouver, Canada; [3]Women's Health Research Institute, Vancouver, Canada

Background: Shorter leukocyte telomere length (LTL) has been reported in HIV^+ adults. Combination antiretroviral therapy (cART), HIV proteins, and chronic inflammation/oxidative stress can all potentially affect telomerase activity and/or LTL, a marker of aging and predictor of lifespan, and pregnancy may modify this effect. To evaluate this we investigated LTL in HIV+ and HIV- pregnant women to distinguish between the possible effects of HIV vs cART on LTL.

Methods: HIV+ (n=108) and HIV- (n=68) pregnant women were enrolled in a prospective cohort study. In most women, relative LTL was assessed at three visits during pregnancy (1st:13-23, 2nd: 23-31, and 3rd: 31-40 weeks of gestation), and for HIV+ women, at delivery and 6 weeks post-partum. At each visit, possible predictors of LTL were examined by linear regression models that included age, HIV/cART status (HIV-, HIV+ on-cART, HIV+ off-cART), ethnicity, hepatitis C virus (HCV) Ab+, and smoking status. Among HIV+ women, on/off cART status was also examined. Paired t-test was used for within woman comparisons.

Results: The HIV+ and HIV- groups were similar in age (31 ± 6 vs. 31 ± 5 years, p=0.49) but there were fewer Black/African Canadians, and HCV Ab+ women in the HIV- group (p<0.001). At the three pregnancy visits, 48, 45 and 44 % of participants reported smoking, with no difference between groups (p=0.24). CART initiation was pre-conception for 23%, 76% started cART during pregnancy and 50% continued post-partum. At 1st visit, smoking (p=0.002) and HIV^+ status (p=0.012), irrespective of cART status, were associated with shorter LTL. At subsequent visits, a similar trend continued but no longer reached significance. No change in LTL was seen between the 1st and 3rd visits in HIV-(p=0.84) or HIV+ women receiving cART at both visits (p=0.11). However, in women who initiated cART after the 1st visit, LTL at 3rd visit was significantly longer (+5.5%, p=0.001) than at the 1st. Post-partum LTL in HIV+ women was significantly shorter (P< 0.0001) than that measured at the 3rd visit, irrespective of post-partum cART status although the effect size was greater among those off cART.

Conclusions: In the context of pregnancy, cART initiation appears to improve LTL, possibly due to reduced inflammation and oxidative stress. Whether the post-partum LTL shortening is related to pregnancy ending or HIV/cART is unclear as post-partum samples were unavailable in controls. Of importance, in addition to HIV, smoking is also independently associated with shorter LTL.

902 Low Prolactin and High 20αHSD May Contribute to cART-Induced P4 Deficits in Pregnancy

Eszter Papp; **Lena Serghides**
AAPH Team
Toronto General Research Institute, Toronto, Canada

Background: Combination antiretroviral therapy (cART) has been linked to small birth weight, preterm delivery and other pregnancy complications. Our earlier results demonstrated that cART exposure was associated with decreased levels of progesterone (P4) mid-pregnancy in HIV-positive (HIV+) cART exposed women, which correlated with

birth weight percentiles. In mice, progesterone supplementation improved fetal weight deficits induced by cART. In this study we investigated the molecular mechanisms leading to cART-associated P4 level alterations.

Methods: Expression levels of key enzymes of P4 synthesis and metabolism were assessed by qPCR on placenta tissue from HIV+ cART-exposed (Study group, N=33) and HIV-negative women (Control group N=15). Plasma P4 and human prolactin (hPL) levels were quantified at gestational week 33-37 by EIA. Human choriocarcinoma (BeWo) cells were treated with increasing doses of hPL for 24h and 20αHSD expression and P4 levels were measured by qPCR and EIA respectively. P4 levels in cART-exposed BeWo cells were assessed with or without 20αHSD inhibition.

Results: Similarly to our findings at mid-gestation, P4 levels were significantly lower in the study group compared to the control group (median [IQR]: 131.0 [93.3-158.9] vs. 171.1 [139.6-198.8] ng/mL respectively, p=0.014). Placental expression of most P4 metabolism enzymes was similar between groups. Only the P4-eliminating enzyme 20αHSD was significantly higher in the study group (Table 1). hPL, the main regulatory hormone for 20αHSD, was significantly lower in the study group compared to controls (median [IQR]: 0.50 [0.38-0.72] vs. 0.77 [0.48-0.89] ng/mL, respectively, p=0.043). 20αHSD expression significantly correlated with hPL levels in women's plasma at GW 33-37 (Spearman's r=-0.822, p<0.0001). In BeWo cells hPL down-regulated 20αHSD expression and P4 production in a dose-dependent manner (p <0.0001). cART exposed BeWo cells produced significantly less P4 compared to controls (median [IQR] 2.8 [2.5-3.1] vs 3.6 [3.5-3.7] ng/mL, p=0.028). P4 levels were restored by inhibiting 20αHSD activity (3.6 [3.4-4.0] ng/mL).

Enzymes	HIV+ cART exposed median [IQR] arbitrary units	HIV-uninfected media [IQR] arbitrary units	p-value
Cyp11A1	16.86 [3.86 - 209.5]	22.5 [6.87 - 81.13]	0.93
Cyp19A1	120.1 [0.89 - 297.2]	198.9 [133.2 - 389.6]	0.20
3βHSD	2.21 [1.70 - 2.88]	2.71 [0.97 - 3.20]	0.65
17βHSD	1.16 [0.61 - 1.82]	0.93 [0.60 - 1.60]	0.70
20αHSD	2.81 [0.89 - 26.1]	1.09 [0.63 - 1.56]	0.0084

Expression levels of P4 metabolism enzymes

Conclusions: Our data suggest that low P4 levels observed in cART-exposed HIV+ pregnant women could be the result of higher levels of 20αHSD induced by low hPL levels. We describe a new mechanism by which cART maybe influencing maternal hormone balance during pregnancy, and identify potential new therapeutic targets that may improve birth outcomes for HIV+ women on cART.

TUESDAY, FEBRUARY 24, 2015

Session P-T10 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Immune Mechanisms in MTCT

903 Generating HIV Neutralization in Milk With Neutralizing IgG/dIgA Antibodies Infusion

Genevieve Fouda[1]; Josh Eudailey[1]; Erika Kunz[1]; Joshua Amos[1]; Jonathan Himes[1]; Lisa Colvin[1]; Xinyue Wang[2]; Keith Reimann[2]; Barton Haynes[1]; Sallie Permar[1]

[1]Duke University, Durham, NC, US; [2]University of Massachusetts Medical School, Boston, MA, US

Background: Breastfeeding is responsible for almost half of infant HIV-1 infections in resource-limited areas. While antiretroviral prophylaxis reduces transmission, it is difficult to implement and does not eliminate the risk of postnatal HIV infection. Inhibition of virus in breast milk by passively-infused broadly neutralizing antibodies (bNab) could be a potential strategy to reduce the infectious virus reservoir in milk. To investigate the distribution of passively-infused bNabs to the breast milk compartment, we assessed the kinetics of binding and neutralizing antibody responses in plasma and milk of lactating rhesus monkeys following passive immunization with the IgG and dimeric IgA (dIgA) forms of the bnAb B12.

Methods: The first generation bnAb B12 Ig variable regions were engineered in either rhesus IgG1Fcs or rhesus IgA Fcs with rhesus J chain. Rhesus recombinant B12 versions were administered intravenously at a dose of 5mg/kg to three (dIgA) or four (IgG) hormone-induced, lactating female rhesus monkeys. Blood and milk were collected prior to and from 1 hour to seven weeks post-infusions. Levels of the infused antibodies and tier 1 (HIV MW965) virus neutralization in TZM-bl cells were measured at each time-point.

Results: B12 IgG and dIgA peaked in plasma 1-6 hours post-infusion, whereas the peak in milk was slightly delayed following IgG infusion (24-72 h) as compared to dIgA infusion (6-24h). The median peak B12 plasma concentration was similar between the two groups of animals (IgG median: 87,503 ng/ml, dIgA median 72,905 ng/ml, p=0.57). In contrast, the peak B12 milk concentration in dIgA infused animals was up to two logs higher than in animals infused with IgG (Median, IgG:59 ng/ml, dIgA: 5,462 ng/ml, p=0.06). Interestingly, both B12 IgG and B12 dIgA were still detectable in plasma and milk seven weeks after infusion. The peak neutralizing activity in plasma occurred 6 to 24h post infusion and was comparable between animals immunized with IgG and dIgA (median ID_{50} against MW965: 2,313.5 versus 1,821, p=0.22). Neutralizing activity peaked in breast milk 24-72 h after IgG infusion and 24 h after dIgA infusion and trended one log higher following dIgA than IgG infusion (median ID_{50} 50.5 versus 526, p=0.06).

Conclusions: Our results indicate distinct kinetics of the transfer of systemic IgG and dIgA bnAbs to the breast milk compartment and suggest that maternal passive immunization with dIgA bNabs may be an effective way to achieve elimination of infectious virus in milk.

904 Specificity of V3-specific Neutralizing Responses in HIV-1 Infected Women

David R. Martinez; Genevieve Fouda; Nathan Vandergrift; Celia LaBranch; David Montefiori; Xiaoying Shen; Thomas Denny; Georgia Tomaras; Sallie Permar

Duke Human Vaccine Institute, Durhamc, NC, US

Background: We recently completed a humoral immune correlate analysis of MTCT risk in the U.S. Women and Infant Transmission study (WITS), a historical cohort followed before availability of antiretroviral therapy. We observed that plasma IgG responses against the Envelope (Env) third variable (V3) loop and tier 1 virus neutralization predicted reduced risk of MTCT. To follow up on this study, we investigated the binding specificity of maternal plasma anti-V3 IgG antibodies and their contribution to the tier 1 virus neutralization response.

Methods: Maternal plasma samples (n=248) were tested for IgG binding against a multi-clade panel of Env V3 peptides by a binding antibody multiplex assay to identify amino acid differences associated with IgG binding strength. A peptide competition neutralization assay with SF162 V3, scrambled and no peptide was used to measure the

contribution of V3-specific antibodies to tier 1 virus (SF162) neutralization in TZM-bl cells. A regression model was used to investigate the association between neutralization titers and MTCT risk.

Results: The maternal plasma V3-specific IgG response against the clade B peptide was high in magnitude (median MFI 23,177), but, binding was abolished (median MFI < 100) against the CRF1 V3 peptide, which differed from clade B peptide at 3 amino acid residues (K305T, I307T and A317R). Moderate plasma binding was observed against the clade A peptide (median MFI 8,739), which differed from the clade B peptide at positions I307V and H308R. Based on the shared amino acid differences between the V3 peptides, positions 305, 307, 308, and 317 flanking the V3 loop tip appear to be critical for maternal plasma V3 binding. Maternal plasma tier 1 virus neutralization significantly decreased in the presence of SF162 V3 as compared to the scrambled peptide and no peptide (median ID_{50} 671, 1399, 2930, for SF162 V3 peptide, scrambled peptide, and no peptide, respectively; p<0.0001 for both). The median plasma tier 1 virus neutralization inhibition with the V3 peptide was 50% (IQR 9-75%), yet the proportion of the maternal plasma neutralization inhibited by the V3 peptide did not predict MTCT risk.

Conclusions: Our results suggest that in clade B HIV-1-infected women, V3 is an important tier 1 virus neutralization epitope that is dependent on residues that flank the V3-loop tip for IgG binding. Yet, additional epitope specificities may also contribute to the maternal neutralization responses associated with decreased MTCT risk.

905 Broad, Highly Avid Vaccine-Elicited Anti-V1V2 IgG Responses in HIV-Exposed Infants

Genevieve Fouda[1]; Coleen Cunningham[1]; Elizabeth McFarland[2]; Bill Borkowsky[3]; Nicole Yates[1]; Erin McGuire[1]; Hua-Xin Liao[1]; Barton Haynes[1]; Georgia Tomaras[1]; Sallie Permar[1]
[1]Duke University, Durham, NC, US; [2]University of Colorado, Aurora, CO, US; [3]New York University, New York, NY, US

Background: We have previously reported that infant vaccination can induce high magnitude and durable HIV-1 envelope (Env)-specific IgG responses, including against the Env V1V2 loops. Importantly, in the trial of the moderately effective RV144 vaccine, anti-V1V2 IgG responses were associated with reduced risk of HIV acquisition. To further characterize this potentially-protective response in infants, we measured the breadth, IgG subclass distribution, and avidity of vaccine-elicited anti-V1V2 IgG.

Methods: In PACTG 230, HIV-exposed infants were immunized with 4 doses of SF-2 rgp120+ MF-59 (Chiron vaccine) or placebo between 0 and 20 weeks of age; 49 Chiron and 18 placebo recipients were included in the present study. Binding antibody multiplex assay (BAMA) was used to measure IgG responses against A244 V1V2 (clade AE), gp70 1086C V1V2 (clade C), gp70 V1V2 B case A2 (clade B), gp70 B case A2 B case A2 V169K, gp70 B case A2 mut3 (V169K/E172V/E173V mutations), and gp70 V1V2 (A) (clade A). IgG1 and IgG3 responses were measured against gp70 B case A2 V1V2 by BAMA. Avidity was measured by ELISA and the avidity index (AI) calculated by dividing the optical density in presence of urea by that without urea.

Results: At birth, vaccine and placebo recipients had similar maternally-acquired anti-V1V2 IgG levels. At peak immunogenicity (week 24), vaccinees had higher frequency and magnitude multiclade anti-V1V2 IgG responses than placebo recipients (p <0.0001 for all antigens). Moreover, the magnitude of IgG responses significantly increased between weeks 0 and 24 in vaccine but not placebo recipients for all antigens except gp70 V1V2 (A), indicating that the vaccine induced antibodies that recognize the V1V2 region across clades. IgG responses against all V1V2 constructs except g70 V1V2 (A) remained higher at week 52 in vaccinees than in placebo recipients (p values from <0.0001 to 0.0083). The majority of infants had detectable levels of anti-V1V2 IgG1 antibodies (week 24: 89%), but 47% also had anti-V1V2 IgG3 at week 24. However the IgG3 response was short-lived. There was no difference in the avidity of the anti-V1V2 IgG that was maternally-acquired (birth) and vaccine-elicited (week 24 in vaccine recipients), with median AI: 0.89 and 0.78 at week 0, and 24, respectively (p=0.15).

Conclusions: Adjuvanted Env vaccination of HIV-exposed infants can induce cross-clade specific, durable anti-V1V2 IgG that have avidity comparable to that of anti-V1V2 IgG acquired from their chronically-infected mothers.

906 Maternal Neutralization Escape Virus Variants Do Not Predict Infant HIV Infection Risk

Caitlin Milligan[1]; Maxwel Omenda[1]; Vrasha Chohan[1]; Katherine Odem-Davis[1]; Barbra A. Richardson[1]; Ruth W. Nduati[2]; Julie M. Overbaugh[1]
[1]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [2]University of Nairobi, Nairobi, Kenya

Background: Mother-to-child transmission (MTCT) of HIV provides a setting in which to study the immune correlates of protection from infection. The role of maternal neutralizing antibodies (NAbs) in preventing MTCT, however, is unclear. Variable findings reported in the literature may be due to challenges in sampling viruses and antibodies near transmission, differences in viruses tested, and availability of key clinical correlates including viral load. We sought to understand whether mothers who transmitted the virus to their infants via breastfeeding differed in their ability to neutralize their autologous virus variants at the time of transmission from mothers who did not transmit.

Methods: HIV-infected mothers from Kenya were included based on the following criteria: 1)high plasma viral load (>4.6$\log_{10}$ copies/mL); 2)breastfed ≥3 months; 3)infant was HIV-DNA negative at birth; 4)maternal sample available prior to, but near the time of transmission. Ten non-transmitting mothers (NTM) and 10 transmitting mothers (TM) were chosen based on these criteria and full-length HIV-1 envelope genes were cloned from PBMCs from each woman. These envelopes were used to generate pseudoviruses that were tested against maternal autologous/contemporaneous plasma in a TZM-bl neutralization assay. We estimated the association between risk of transmission and the $\log_2$IC50 for multiple virus variants per mother using logistic regression with clustered standard errors to account for intra-woman correlation. A t-test was used to compare the proportion of neutralization-resistant viruses in TM and NTM.

Results: In total, 100 envelope genes were cloned from the 20 women (5 per woman) and displayed a range of neutralization sensitivities when tested as pseudovirus against maternal plasma. TM had a median $\log_2$IC50 of 8.20 (IQR 7.58, 9.01) and NTM had a median of 7.82 (IQR 6.56, 9.02). In a logistic regression, there was not a significant difference in autologous NAb responses between TM and NTM (OR 1.25, p=0.3). Neutralization-resistant viruses were detected in both groups at similar proportions when tested against autologous plasma at a 1:50 dilution (NTM 6% vs. TM 2%, p=0.3).

Conclusions: HIV-infected mothers exhibit a mixture of mostly neutralization-sensitive viruses, however, both TM and NTM also harbor neutralization resistant variants around the time of transmission. These results suggest that MTCT during the breastfeeding period is not simply due to the presence of maternal neutralization escape variants.

TUESDAY, FEBRUARY 24, 2015

Session P-T11 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

PMTCT-Associated Drug Resistance in Women and Infants

907 ART Failure and Resistance Among Pregnant and Post-Partum Women in South Africa

Christopher J. Hoffmann[1]; Silvia Cohn[1]; Fildah Mashabela[2]; Jennifer Hoffmann[1]; **Kelly E. Dooley**[1]; Richard E. Chaisson[1]; Neil Martinson[2]
the TSHEPISO Study Team

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Perinatal HIV Research Unit (PHRU), Johannesburg, South Africa

Background: In South Africa, 30% of pregnant women presenting for antenatal care are HIV-infected, many of whom are started on antiretroviral therapy (ART). Postpartum adherence and retention may be compromised by system limitations and patient-level factors. Increased loss from care, failed transitions in care, treatment failure, and acquired drug resistance may result when adherence to medications or visits diminishes.

Methods: Tshepiso is a prospective study of HIV-infected pregnant women with and without active TB disease in Soweto, South Africa. Women are enrolled prenatally, and mother-infant pairs are followed for 12 months postpartum. CD4 count and viral load are evaluated at all study visits. HIV drug resistance was performed on 12-month postpartum specimens with an HIV RNA >1000c/mL. We compared pre and post-partum virologic suppression (defined as HIV RNA <400 c/mL) and CD4 count change among 103 women who were in care and receiving ART both pre-partum and postpartum.

Results: At enrollment for the 103 women, the median age was 29 years, gestational age 29 weeks, CD4 count was 317 cells/mm^3; 43 (42%) women were co-infected with TB, and 23 (22%) were on ART prior to pregnancy. During pregnancy, 93 (87%) women had an HIV RNA <400 c/mL compared to 73 (71%) at 12 months postpartum (McNemar's, p<0.001). From delivery to one year post-partum, women with a suppressed HIV RNA had an increase in CD4 count to a median of 480 cells/mm^3 (IQR: 374, 625) while women without suppression at 12 months had a decline to a median of 278 cells/mm^3 (IQR: 224, 330) (Kruskal Wallis, p<0.001); both groups started with a pre-partum median CD4 count of 300 cells/mm^3. Plasma samples for 28 of the 30 women with viral load >1000 copies/mL at 12 months were tested for HIV drug resistance; 25 were amplified. 12 (48%) had major resistance mutations: all 12 had NNRTI resistance, 4 (16%) had an M184V mutation. Among the 25 women, resistance at 12 months was associated with pre-partum HIV RNA >400 c/mL (p=0.003) but was not associated with TB treatment or timing of ART initiation.

Conclusions: The proportion of women with HIV virologic suppression dropped substantially from delivery to 12 months post-partum and was associated with HIV drug resistance and lower CD4 counts. Regimen selection for future PMTCT and re-engagement in care must take this into account. Improved strategies to support post-partum adherence, especially among those without complete virologic suppression during pregnancy, are needed.

908 High Prevalence of HIV-1 Drug-Resistance Mutations in Subtype C Transmitting Mothers Detected Using 454 Ultra-Deep Sequencing

Johanna Ledwaba[1]; Anna Salimo[1]; Karl Technau[4]; Simon Travers[3]; Lynn Morris[1]; Gillian Hunt[1]; Louise Kuhn[2]

[1]National Institute for Communicable Diseases, National Health Laboratory Service, Sandringham, South Africa; [2]Columbia University, New York, NY, US; [3]University of the Western Cape, Modderdam, South Africa; [4]University of the Witwatersrand, Johannesburg, South Africa

Background: In 2010, new PMTCT guidelines were implemented in South Africa wherein pregnant women with CD4 count <350 cells/ml received HAART (Option B) and women with CD4 count >350 cells/ml received antenatal and intrapartum prophylaxis (Option A). In this study we performed 454 ultra deep pyrosequencing to determine the prevalence of maternal drug resistance variants in HIV-1-transmitting mothers after guideline changes were implemented.

Methods: The Finding Infants with HIV Disease: Evaluation of Resistance, pMTCT Failures and Linking Access to Care (FInHDER) Study, conducted in 5 clinics and hospitals in Johannesburg in 2011, set out to recruit treatment-naive HIV-infected infants and children >2 years of age presenting at routine PMTCT follow-up clinics and inpatient services. The study recruited mothers and infants who had full, partial or no access to PMTCT. As part of this study, 204 maternal plasma samples were collected and sequenced for HIV drug resistance mutations using ultra-deep pyrosequencing technology and 454 prototype plates containing lyophilized MID tagged primers. Sequence reads were analyzed using 454 AVA software and Seq2Res pipeline.

Results: Of the 204 women, 116 had received PMTCT, 66 had received no PMTCT, 15 were receiving cART, and 10 had unknown exposure. Ultra deep sequencing by 454 was successful in 200 (98%) specimens. A total of 80 specimens (41.8%) had HIV-1 drug resistance detected by 454 UDPS: NNRTI mutations were detected in 68 (34%) specimens, NRTI mutations in 17 (9%), and dual-class resistance in 13 (7%). Single PI mutations were identified in 12 specimens. When stratified by age of child, NNRTI mutations were present in 17.2% (11.4 – 25.1%) of women in the exposed group whose time since childbirth was <6 months versus 6.1% (2.4 – 14.6%) in the unexposed group. Lower rates of NNRTI mutation were present between 6 months and 1 year [3.4% (1.3-8.5%)] and up to 2 years [2.6% (0.9-7.3%)] post exposure in the exposed group. However, in the unexposed group the NNRTI mutation rate remained constant [4.5% (1.6-12.5%)]. NNRTI resistance was driven by the K103N (n= 28, 24.3%) and Y181C (n=11, 9.5%) mutations in the exposed group, and by K103N (n=4, 5.4%) in the unexposed group.

Conclusions: These data highlight the value of ultra-deep sequencing to reveal the presence of resistance mutations in transmitting mothers suggesting poor compliance and/or regimen failure during PMTCT exposure.

909 NVP Resistance in Infants Infected by HIV-1 via Breastfeeding in the BAN Study

Julie A. Nelson[1]; Ali Fokar[1]; Michael G. Hudgens[1]; Kara J. Compliment[1]; Gerald Tegha[2]; Deborah Kamwendo[2]; Athena P. Kourtis[3]; Denise J. Jamieson[3]; Charles M. van der Horst[1]; Susan A. Fiscus[1]

[1]Univ of North Carolina at Chapel Hill, Chapel Hill, NC, US; [2]University of North Carolina Project–Malawi, Lilongwe, Malawi; [3]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: The Breastfeeding, Antiretrovirals, and Nutrition (BAN) study showed that treatment of HIV-1-infected mothers (maternal antiretroviral (ART) arm) or prophylaxis of their infants (infant nevirapine (NVP) arm) for up to 28 weeks of breastfeeding were both effective in preventing HIV transmission via breastfeeding. In addition to the study interventions, all mothers and infants received single dose NVP during delivery and one week of AZT/3TC post-delivery to reduce NVP resistance. We assessed resistance in the infected infants from the 3 arms of the BAN study.

Methods: The latest available plasma sample for each infant enrolled in BAN who was infected 2-48 weeks postpartum was sequenced: 23 transmissions in the infant NVP arm [mean 24 weeks prophylaxis], 23 transmissions in the maternal ART arm [mean 26 weeks ART], and 34 transmissions in the control arm. Subtype C-specific primers were used for reverse transcription and nested PCR. Population sequencing was performed to identify resistance mutations in the RT gene. Available maternal plasma close to the time of each infant's infection was sequenced for each case of infant NVP arm transmissions as well as for infants in the other arms with identified NVP resistance.

Results: HIV-infected infants in the infant NVP arm were significantly more likely to have NVP resistance than infected infants in the other two arms of the trial, especially during breastfeeding through 28 weeks of age (50% in infant NVP arm vs. 6.3% in maternal ART arm and 10.7% in control arm, p=0.01). There was a nonsignificant trend toward higher

prevalence of NVP resistance with longer times between acquisition of infant HIV infection and cessation of NVP prophylaxis. Most of the infants (69%) with NVP resistance had different mutations than their mothers carried.

Conclusions: Infants on NVP prophylaxis during breastfeeding are at reduced risk of acquiring HIV, but are at increased risk of NVP resistance if they do become infected. The rate of NVP resistance in the infant NVP arm of BAN (50%) was lower than that observed with NVP prophylaxis in the SWEN (92%), PEPI-Malawi (76%), and HPTN 046 (74%) studies, and may have been due to fewer mothers carrying NVP resistance after receiving AZT/3TC for a week after their single-dose NVP. These findings point to the need for frequent HIV diagnostic testing of infants while on NVP prophylaxis, and for availability of antiretroviral regimens excluding NVP for treating infants who become infected while on such a prophylactic regimen.

TUESDAY, FEBRUARY 24, 2015

Session P-U1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HIV Diagnosis in Infants and Children

910 Birth HIV PCR Testing in South Africa: Diagnostic Challenges and Risk Factor Analysis

Karl-Günter Technau[1]; Louise Kuhn[2]; Lucia Hans[3]; Sergio Carmona[3]; Ashraf Coovadia[1]; Gayle Sherman[4]

[1]University of the Witwatersrand, Johannesburg, South Africa; [2]Columbia University, New York, NY, US; [3]National Health Laboratory Service, Johannesburg, South Africa; [4]National Institute for Communicable Diseases, Johannesburg, South Africa

Background: The South African Prevention of Mother to Child Transmission program reported infant HIV transmission rates at 6 weeks of 2% in 2013. Since a large proportion of HIV infections can be detected at birth, testing at this time could facilitate earlier treatment and thereby reduce HIV-related morbidity and mortality.

Methods: From Sept 2013, Rahima Moosa Mother and Child Hospital in Johannesburg, South Africa, provided birth HIV PCR testing for low birth weight or preterm neonates in accordance with national guidelines (era A). From June 2014 (era B) all HIV-exposed neonates were tested (weekend cover commencing Aug 2014). The Roche COBAS® TaqMan® HIV-1 Qual Test (Versions 1 and 2 in era A and B respectively) was used. Results are returned ~1 week from birth and all neonates with positive or indeterminate results are followed. PCR negative neonates are referred for routine testing at 6 weeks. Here we describe coverage, transmission rates and risk factors for transmission.

Results: Over 9 months in era A, 16% (193/1240) of all HIV-exposed neonates (66% [193/261] of targeted neonates) were offered testing with 100% uptake. Over 4 months in era B, 90% (675/750) of all HIV-exposed neonates were offered testing with 99% uptake. In era A, 6.7% (13/193) (95% CI: 3.2-10.3) of infants tested PCR positive (n=9) or indeterminate (n=4) with 38% (5/13) female. In era B, 2.1% (14/663) (95% CI: 1.0-3.2) tested positive (n=10) or indeterminate (n=4) and 86% (12/14) were female (p=0.018). Further testing of 8 neonates with indeterminate results found detectable HIV RNA or positive qualitative results in six. Two infants (both in era B) have had only negative HIV results on subsequent tests. All of the children with positive birth tests subsequently had at least one positive qualitative PCR or quantitative HIV RNA assay. The median highest HIV RNA quantity was 5.7 log copies/ml (IQR: 4.0-6.0) in era A and 3.2 log copies/ml (IQR: 2.2-4.5) in era B (p=0.009).

Table 1: Risk factor analysis amongst 663 neonate/mother pairs in era B with 14 positive or indeterminate cases and 649 negative HIV PCR birth results

Risk Factor	Prevalence of risk factor	n (%) of cases detected if testing targeted this risk factor only	% (n/N) Case prevalence with risk factor present	% (n/N) Case prevalence with risk factor absent	p-value
Mother had ART for < 12 weeks	25.9%	7 (50.0%)	4.1% (7/172)	1.4% (7/491)	0.059
Poor adherence reported	2.9%	0 (0%)	0% (0/15)	2.2% (11/486)	1.0
Mother diagnosed >28 weeks gestation	14.3%	4 (28.6%)	4.3% (4/93)	1.8% (10/559)	0.13
Maternal VL >1000 copies/ml	11.4%	1 (7.1%)	20% (1/5)	7.7% (3/39)	0.39
Preterm (<37 weeks)	29.2%	6 (42.9%)	3.2% (6/188)	1.8% (8/456)	0.25
Low birth weight (<2,5kg)	20.8%	3 (21.4%)	2.2% (3/138)	2.1% (11/525)	1.0
TB during pregnancy	0.5%	0 (0%)	0% (0/3)	2.1% (14/657)	1.0
Targeted testing using a combination of any of the above risk factors	52.3%	9 (64.3%)	2.6% (9/347)	1.6% (5/316)	0.43

Conclusions: We achieved excellent coverage with universal birth testing revealing a transmission rate similar to that reported by national statistics at 6 weeks. Targeted testing would require testing ~half (52.3%) the exposed neonates but would miss ~third of infected neonates. A less sensitive PCR test and/or a higher risk population may account for higher HIV RNA values and fewer diagnostic dilemmas in era A. The high percent of girls in era B requires further investigation. Diagnostic problems raised by indeterminate results require urgent attention.

911 System Gaps Result in Late Diagnosis and Treatment of Children With HIV in Hospital

Irene N. Njuguna[3]; Anjuli D. Wagner[1]; Vincent Otieno[3]; Lisa Cranmer[2]; Judy Adhiambo[3]; Sarah Benki-Nugent[1]; Elizabeth Maleche-Obimbo[3]; Jennifer A. Slyker[1]; Dalton Wamalwa[3]; Grace John-Stewart[1]

[1]University of Washington, Seattle, Kenya; [2]Emory University School of Medicine, Atlanta, GA, US; [3]University of Nairobi, Nairobi, Kenya

Background: The pediatric HIV linkage to care cascade has health systems bottlenecks that require improvement. Despite scale up of PMTCT programs, a substantial number of infants still acquire HIV and are diagnosed when hospitalized through provider initiated testing and counseling (PITC). To identify gaps in pediatric linkage to care, we evaluated maternal HIV testing and child hospitalization history for hospitalized children who were diagnosed with HIV for the first time or who were not on ART at hospitalization.

Methods: We identified HIV-infected, ART naïve children aged 0-12 years at Kenyatta National Hospital, Kisumu East District Hospital and Jaramogi Teaching and Referral Hospital and reviewed their PMTCT and past medical history. This was part of an ongoing clinical trial (NCT02063880). HIV infection was determined by rapid HIV test among those over 18months of age and DNA-PCR for those under18 months. We summarized continuous variables using medians and categorical variables using proportions.

Results: Among 173 HIV infected ART naïve children, median age was 2.3 years (IQR 1.3, 4.5). Most (72%) of their mothers had been tested for HIV during pregnancy with higher testing rates in lower age groups [age <18 months (86%), 1.5-5 years (73%), 5-8 years (44%), and 8-12 years (56%) (p=0.01)]. Seventy one (57%) of mothers tested HIV negative during pregnancy. Of the 51(41%) of mothers who tested positive, 34 (67%) of mothers and 18 (35%) of infants received ARV's for PMTCT. Almost all infants (97%) had breastfed.

More than a third of all the children 67(39%) had previous hospitalizations, with 25 (38%) having multiple hospitalizations. Of 85 children previously tested for HIV, nearly half 39(49%) had tested HIV positive but had not initiated ART.

Demographic characteristics, PMTCT and medical history of all children and by age group

	All N=173	0-1.5years (N=58)	1.5-5years (N = 74)	5-8 years (N = 25)	8-12 years (N = 16)
	Median (IQR) or N (%)				
Age (years)	2.3(1.3, 4.5)	0.8(0.3, 1.2)	2.7(2, 3.7)	6.5(6, 6.9)	9.5(9, 11.3)
Mother tested for HIV in pregnancy	124 (72)	50(86)	54(73)	11(44)	9(56)
HIV test negative*	71(57)	23(46)	35(65)	7(70)	6(67)
HIV test positive*	51(41)	27(54)	17(31)	4(30)	3(33)
Mum received ART in pregnancy n=51	34(67)	21(78)	10(59)	2(50)	1(33)
Child received ART for PMTCT n=51	18(35)	9(33)	7(41)	1(25)	1(33)
Child previously hospitalized	67(39)	12(21)	34(46)	14(56)	7(44)
Hospitalized >once	25(38)	3(25)	14(41)	4(29)	4(67)
Child previously tested	85(50)	24(42)	39(53)	12(48)	10(71)
HIV test positive	39(49)	8(33)	17(44)	7(58)	7(70)

*Results unknown for 2 mothers

Conclusions: Current systems often fail to detect HIV among women who acquire the infection after a negative test at PMTCT. Pediatric HIV testing and linkage may not occur even after hospitalization. Repeat maternal HIV testing, routine PITC and prompt linkage to care is necessary to prevent late identification of HIV-infected children.

TUESDAY, FEBRUARY 24, 2015

Session P-U2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Early ART and HIV Persistence

912 Early Infant Antiretroviral Therapy Reduces Transcriptionally Active HIV Persistence

Gert U. van Zyl[1]; Margaret A. Bedison[2]; Anita Janse van Rensburg[3]; Barbara Laughton[3]; Mark F. Cotton[3]; John W. Mellors[2]

[1]Stellenbosch University and National Health Laboratory Service, Parow, South Africa; [2]University of Pittsburgh, Pittsburgh, PA, US; [3]Stellenbosch University and Tygerberg Academic Hospital, Cape Town, South Africa

Background: Early combination antiretroviral therapy (cART) has been shown to reduce the number of HIV-1 DNA containing cells in blood but it is not known how the timing of cART initiation impacts transcriptionally active proviruses or persistent low level plasma viremia. We therefore investigated multiple measures of HIV-1 persistence in children from the "Children with HIV Early Antiretroviral Therapy" (CHER) cohort

Methods: Twenty children were studied from the post CHER cohort, 7-8 years old and on cART for 79-96 months, who received continuous cART either from before (n=12) or after (n=8) 2 months of age and who had HIV-1 RNA suppressed (<400 copies/ml). Longitudinal PBMC and plasma samples were assayed by subtype C-specific quantitative PCR for cell associated HIV-1 DNA (CAD), cell associated HIV-1 RNA (CAR) and plasma HIV-1 RNA with primers and probes targeting a highly-conserved region of *integrase*.

Results: The median (inter quartile-range (IQR)) CAD and CAR levels were significantly lower ($p<0.01$) in children who initiated cART at <2 months of age (early) compared to ≥2 months of age (later): 48 (IQR: 10-94) versus 216 (135-473) HIV-1 DNA copies/million PBMC; and 5 (4-37) versus 436 (48-994) HIV-1 RNA copies/million PMBCs, respectively. One of 12 early treated children had undetectable CAD, versus none of 8 late-treated and 7 out of 12 early treated children had undetectable CAR versus 1 out of 8 ($p=0.07$). Median plasma HIV-1 RNA was lower in children starting cART at < 2 months (0.5 copies/ml; IQR: 0.5-1.1) compared to children starting cART at ≥2 months (1.2 copies/ml; IQR: 0.5-2.8; $p=0.16$). Similarly, 9 of 12 early-treated had undetectable plasma HIV-1 RNA (<0.6 copies/ml) compared to 3 of 8 later treated ($p=0.17$). Comparisons of CAD, CAR and HIV plasma RNA in early- vs later-treated children are shown in Figure 1.

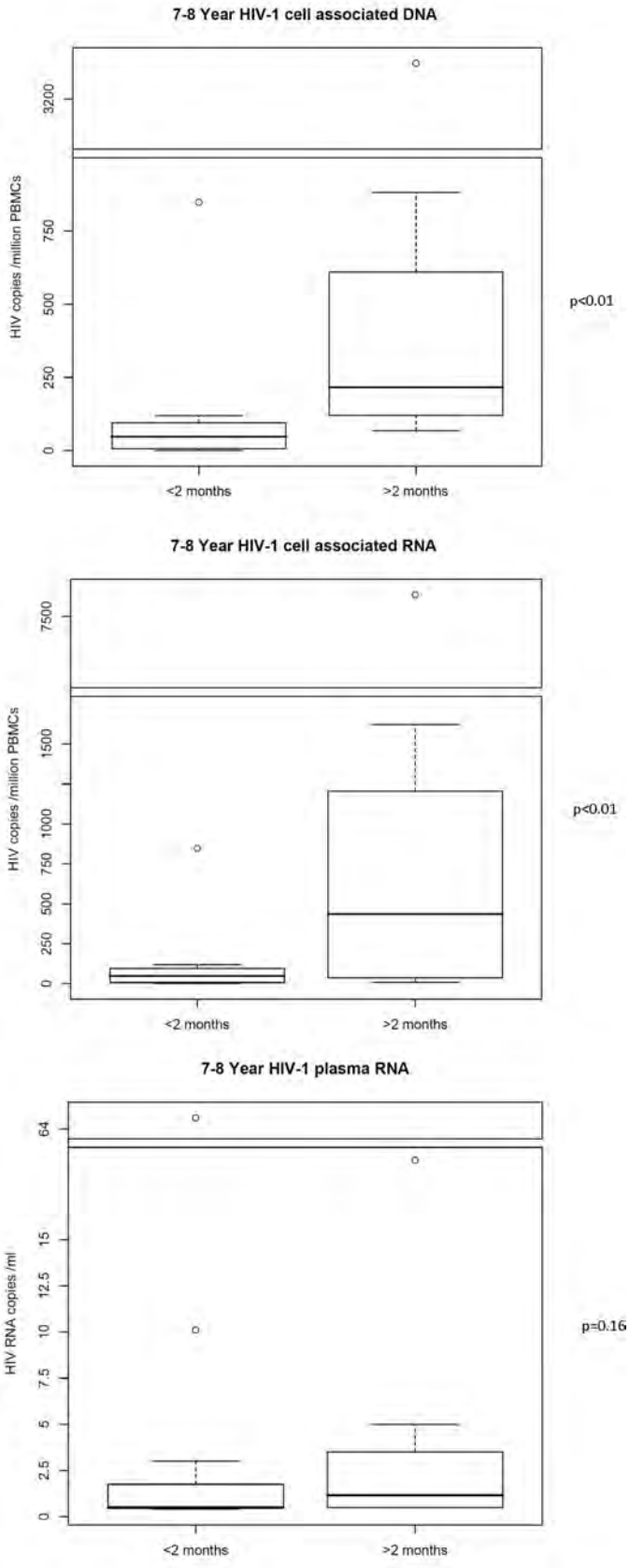


Figure 1: Boxplots of CAD, CAR and plasma HIV-1 RNA in patients at 7-8 years of age who were initiated on cART before or after 2 months of age

Conclusions: This study, in a South African cohort of children, is the first to show that early cART (<2 months of age) compared to later initiation is associated with significant reductions in HIV-infected cells and cell-associated HIV-1 RNA transcripts in blood. Whether reduced HIV-1 persistence from early cART improves responses to curative interventions is unknown and warrants investigation.

WEDNESDAY, FEBRUARY 25, 2015

Session P-U3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Treatment Outcomes Among Children and Youth With HIV

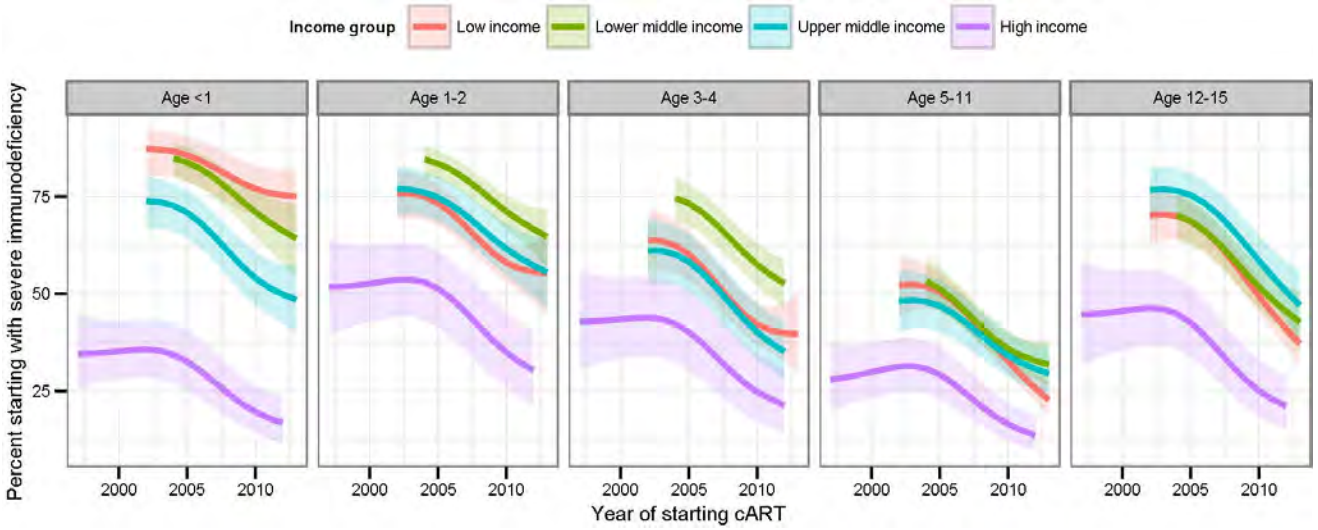
913 Immunodeficiency at the Start of ART in Children: A Global View

Klea Panayidou[1]; Ali Judd[3]
On behalf of the IeDEA Collaboration and the COHERE Collaboration
[1]*University of Bern, Bern, Switzerland;* [2]*University of Copenhagen, Copenhagen, Denmark;* [3]*University College London, London, United Kingdom*

Background: The CD4 cell count or percent (CD4%) at the start of combination antiretroviral therapy (cART) are important prognostic factors in children starting therapy and a key indicator of program performance. We describe trends in percentages of children with severe immunodeficiency at cART initiation in children from low-, middle- and high-income countries.

Methods: Data from the International epidemiologic Databases to Evaluate AIDS (IeDEA) from the Caribbean, Central and South America (CCASA), Asia-Pacific, and West, Central, East and Southern Africa and from the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) were analyzed. Patients aged <16 years with known sex were eligible. Analyses were stratified by World Bank country income classification (as of 01/2013), age group (<1, 1-2, 3-4, 5-11, 12-15 years), sex and country. Missing CD4 counts and CD4% were multiply imputed. Weighted generalized additive mixed models were used to smooth the percentage starting with severe immunodeficiency over the years. Fitted/predicted percentages were aggregated using Rubin's rules. Severe immunodeficiency was defined by WHO criteria as CD4% <25% (age <12 months), <20% (12-35), <15% (36-59) and CD4 count <200 cells/μl or CD4% <15% in children aged >5 years.

Results: A total of 43,071 patients from 31 countries were included: 37,006 children from sub-Saharan Africa (18 countries), 1,811 from Europe (4), 3,268 from Asia-Pacific (6) and 986 from CCASA (3). Trends in percentages of children starting with severe immunodeficiency from 2002, when ART was scaled up globally, varied by age and country income group (figure). In 15 countries 50-74% of children had severe immunodeficiency in 2013: Benin, Burkina Faso, Cambodia, Ghana, India, Indonesia, Malaysia, Mali, Mozambique, Senegal, United Republic of Tanzania, Thailand, Uganda, Vietnam, Zimbabwe. In 13 countries the percentage in 2013 was 25-49%: Brazil, DRC, Côte d'Ivoire, Haiti, Kenya, Lesotho, Malawi, Peru, Rwanda, South Africa, Togo, United Kingdom, Zambia. In 3 countries it was <25% in 2013: France, Netherlands, Spain.



Conclusions: Despite progress in many low- and middle-income countries, many children continue to start cART with severe immunodeficiency. Early diagnosis and treatment of HIV-infected children to prevent morbidity and mortality associated with immunodeficiency must remain a global public health priority.

914 Immune Recovery at 5 Years on ART in HIV+ Children From Four African Countries

Chloe A. Teasdale; Ruby Fayorsey; Zenebe Melaku; Duncan Chege; Catarina Casalini; Thresia Sebastian; **Elaine J. Abrams**
ICAP at Columbia University, New York, NY, US

Background: By 2012 more than 640,000 children were receiving antiretroviral therapy (ART) worldwide but there are few descriptions of long term treatment outcomes in children enrolled in routine service programs in sub-Saharan Africa. We examined immune recovery after 5 years on ART in children in Ethiopia, Kenya, Mozambique and Tanzania.

Methods: Routinely collected patient level data were used to describe HIV-infected children 0-14 years(yrs) enrolled at ICAP-supported sites 2005-2009 with >=5yrs of follow-up. Data came from the Optimal Models study and were de-identified prior to analysis. We examined the proportion of children on ART who achieved immune recovery defined as CD4 cell count (CD4) >=500 cells/mm^3. Relative risk regression was used to examine factors associated with immune recovery adjusting for country, year of enrollment, gender, and age, CD4, WHO stage and regimen at ART initiation.

Results: 22,814 children were enrolled in care at 185 health facilities with median age of 4yrs [interquartile range(IQR):2-8]; 11,187 (49.0%) started ART, 6,961 (30.5%) were lost to follow-up, 1,034 (4.5%) died and 1,676 (7.3%) transferred before ART. 3,270 (29.2%) children who started ART and had >=5yrs of follow-up (median follow-up was 6yrs[IQR:5-7]). At ART initiation, 11.3% were <2yrs, 29.4% were 2-4yrs, 38.5% were 5-9yrs and 20.8% were 10-14yrs of age. Median CD4 was 256 [IQR:129-503] at ART initiation and 730 [IQR 430-1065] at the last CD4 during follow-up. Immunologic recovery was observed in 67.5% of children. Children <5yrs at ART initiation were 20% more likely to achieve immune recovery (adjusted risk ratio (aRR) 1.2, 95%CI 1.1-1.3, p<0.0001) and those with CD4>=200 at ART initiation were 30% more likely to have immune recovery (aRR 1.3, 95%CI 1.2-1.4, p<0.0001). Children initiating treatment with a D4T-based ART regimen were 10% more likely to have immune recovery compared to those starting AZT-based regimens (aRR 1.1, 95%CI 1.1-1.2, p<0.0001).

Conclusions: In this large cohort of children from sub-Saharan Africa, only half initiated ART and 35% died or were lost before starting ART. Among those who started ART and had 5 years of follow-up, many achieved immune recovery which was associated with younger age, higher CD4 and D4T-based ART regimen at ART initiation. These findings are in keeping with previously reported study cohorts and represent important data on children enrolled in routine service programs in resource limited settings.

915 Antiretroviral Therapy in Severely Malnourished, HIV-Infected Children in Asia

David C. Boettiger[1]; Linda Aurpibul[2]; Dina Muktiarti[3]; Siew Fong[4]; Pagakrong Lumbiganon[5]; Saphonn Vonthanak[6]; Nguyen Van Lam[7]; Rawiwan Hansudewechakul[8]; Azar Kariminia[1]
On behalf of TREAT Asia Pediatric HIV Observational Database

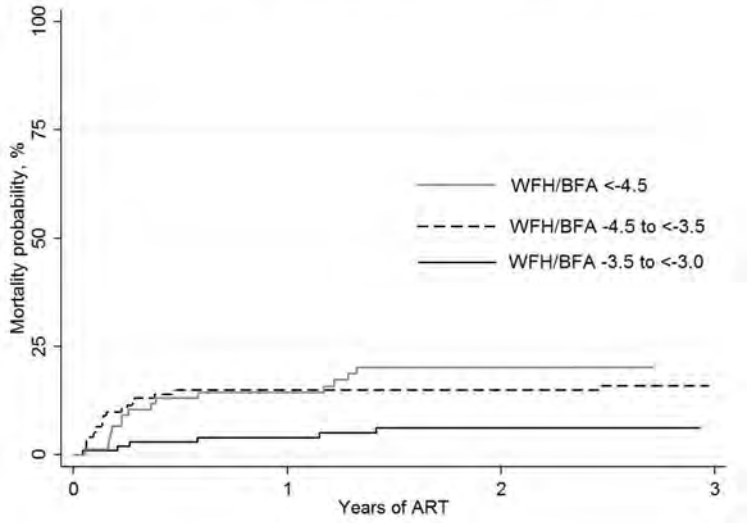
[1]University of New South Wales, Sydney, Australia; [2]Chiang Mai University, Chiang Mai, Thailand; [3]Cipto Mangunkusumo General Hospital, Jakarta, Indonesia; [4]Hospital Likas, Kota Kinabalu, Malaysia; [5]Khon Kaen University, Khon Kaen, Thailand; [6]National Centre for HIV/AIDS Dermatology and STDs, Phnom Penh, Cambodia; [7]National Hospital of Pediatrics, Hanoi, Viet Nam; [8]Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand

Background: In HIV-infected children with severe malnutrition (SM), guidelines recommend that antiretroviral therapy (ART) is initiated soon after SM stabilization but information on ART use in this population is lacking. We evaluated growth, CD4% recovery, toxicity-associated ART modification and death in children with SM at ART initiation.

Methods: Children enrolled in the TREAT Asia Pediatric HIV Observational Database who initiated ART with a weight-for-height z-score (WFH)<-3 if aged 6-60 months or body mass index-for-age z-score (BFA)<-3 if aged 61 months-14 years were included. Generalized estimating equations were used to investigate poor growth response (weight-for-age z-score<-3) and poor immune response (CD4%<25), and competing risk regression was used to analyze mortality and toxicity-associated treatment modification.

Results: The SM definition was met by 310 (12%) of 2559 children starting ART with height and weight data available. Median age was 6.6 years, 60% were male, and median WFH/BFA was -3.8. Most initiated stavudine (64%) or zidovudine-based (30%) therapy. Periods of ART start were 2003-06 (45%), 2007-10 (44%) and 2011-13 (11%). Mean weight-for-age z-score increased on ART from -5.8 at initiation to -3.6 after 6 months, -2.9 after 12 months, -2.5 after 24 months, and -2.5 after 36 months. Age 61 months-14 years (OR 2.4 vs. 6-60 months, 95%CI 1.6-3.5, p<0.01) and prior tuberculosis diagnosis (OR 1.6 vs. none, 95%CI 1.1-2.4, p=0.03) predicted poor growth response. Mean CD4% increased on ART from 7.7 at baseline to 14.7 after 6 months, 20.2 after 12 months, 25.1 after 24 months, and 26.6 after 36 months. Poor immune response was associated with baseline CD4% (OR 10.9 for <10 vs. ≥10, 95%CI 6.4-18.7, p<0.01), age (OR 2.13 for 61 months-14 years vs. 6-60 months, 95%CI 1.4-3.2, p<0.01) and male sex (OR 1.5, 95%CI 1.0-2.2, p<0.05). Forty three deaths occurred at a rate of 3.0 per 100 patient-years. Lower baseline WFH/BFA (HR 3.5 for <-4.5 vs. -3.5 to <-3.0, 95%CI 1.4-8.6, p<0.01) predicted mortality (Figure 1). Twenty toxicity-associated ART modifications occurred at a rate of 2.6 per 100 patient-years and rates did not differ by baseline WFH/BFA strata (p=0.88).

Figure 1 - Mortality in children with severe malnutrition at antiretroviral therapy initiation



Conclusions: HIV-infected children with SM experienced rapid growth and immune recovery after starting ART, particularly when started at a young age. ART initiation at a less pronounced stage of SM increased survival but this did not appear to be due to more ART toxicity in children with lower WFH/BFA.

916 Pubertal Development in HIV-Infected African Children on First-Line Antiretroviral Therapy

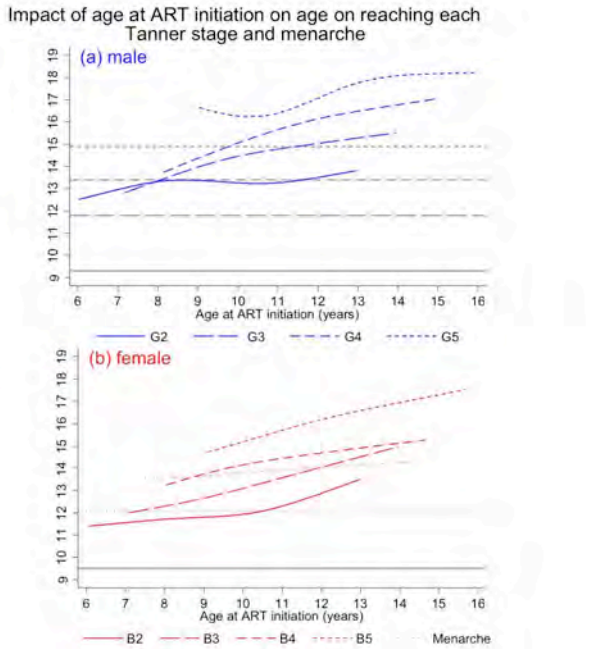
Mutsa F. Bwakura Dangarembizi
On behalf of the ARROW Trial Team

University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe

Background: HIV has been associated with pubertal delay but data on the impact of initiating combination ART in older childhood are limited, particularly in sub-Saharan Africa.

Methods: In the ARROW trial in Uganda/Zimbabwe, puberty was assessed by Tanner staging of genitalia (G1=prepubertal to G5=adult) in males, or breasts (B1 to B5) in females every 24 weeks from age 10 years; menarche every 12 weeks and height every 4-6 weeks. Age at attaining different Tanner stages was estimated using normal interval regression, considering the following predictors using multivariable regression: centre, initial ART regimen, CD4/no CD4 monitoring; age, CD4, WHO stage, height/BMI-for-age at ART initiation; and change in height/BMI-for-age during the first 6 months on ART. Growth was estimated using multi-level models with child-specific intercepts and trajectories.

Results: 582 children were included: median age at ART initiation was 9.4 years (IQR 7.8,11.3); median CD4 was 234 cells/mm^3 (IQR 102,349). At the first assessment, the majority (80.2%) were in Tanner stage 1; median follow-up with staging was 2.8 years. There was a strong delaying effect of older age at ART initiation on age at attaining all Tanner stages (p<0.05) and menarche (p=0.02); but being one year older at ART initiation had different impacts on pubertal delay depending on the specific age at ART initiation (i.e. effects were non-linear; Figure). For example, a boy initiating ART aged 9 would expect to reach G2/G3/G4/G5 at age 13.4/14.0/14.4/16.7 years compared to 13.3/14.8/15.7/16.4 if initiating aged 11. Similarly a girl initiating aged 9 would expect to reach B2/B3/B4/B5 aged 11.8/12.7/13.7/14.7 compared to 12.3/13.6/14.5/15.7 aged 11. In boys, the delaying effect generally attenuated with older age. There were additional pubertal delays associated with greater pre-ART impairments in height-for-age Z-score (p<0.05) and BMI-for-age in girls (p<0.05). There was no evidence that pre-ART immune suppression independently delayed puberty or menarche. However, older children/adolescents had significant growth spurts in intermediate Tanner stages, and height continued to increase significantly even in Tanner stage 5 (p<0.01).



*For a Zimbabwean child with height- and BMI-for-age -2 and -1 at ART initiation **and -2 and -0.7** six months after ART initiation
Gray lines indicate overall mean/median age on reaching each Tanner stage and menarche in Black American US children where available

Conclusions: Delaying ART initiation until older childhood substantially delays pubertal development and menarche, independently of immune-suppression. Factors other than CD4, such as pubertal development, need consideration when making decisions about timing of ART initiation in older children.

917 Mortality of HIV-Infected Youth in the Combination Antiretroviral Therapy (cART) Era

Gayatri Mirani[1]; Paige L. Williams[2]; Miriam Chernoff[2]; Mark Abzug[6]; Myron Levin[3]; James Oleske[4]; George Seage[2]; Rohan Hazra[5]; Russell B. Van Dyke[1]
On behalf of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network P1074 Study Team

[1]Tulane University Health Sciences Center, New Orleans, LA, US; [2]Center for Biostatistics in AIDS Research Harvard School of Public Health, Boston, MA, US; [3]University of Colorado Anschutz Medical Campus, Aurora, CO, US; [4]Division of Pediatrics Allergy, Immunology & Infectious Diseases, Newark, NJ, US; [5]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US; [6]University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO, US; [7]IMPAACT Operations Center FHI 360, Durham, NC, US

Background: cART has resulted in a decrease in HIV-related opportunistic infections and deaths. However, deaths from infectious and non-infectious conditions continue to occur. We reviewed deaths in IMPAACT P1074, a recent prospective cohort study of HIV-infected youth, to characterize those dying with HIV.

Methods: IMPAACT P1074 is a prospective, multicenter surveillance study of long-term outcomes in HIV-infected infants, children, and adolescents. HIV-infected youth enrolled in previous IMPAACT studies were enrolled between April 2009 and June 2013. Annual chart abstractions were conducted to collect demographics, antiretroviral therapy, heights and weights, CD4 counts, HIV viral loads, clinical diagnoses and deaths. Details of deaths were recorded on a study form and autopsy reports were reviewed when available. We compared demographic and health characteristics of those who died and those who survived through June 2014.

Results: Of 1201 subjects, 87% were perinatally infected with a mean age of 20.6 years at last chart review. There were 28 deaths (mortality rate 7.1/1000 person years), with 3 deaths in 2010, 3 in 2011, 14 in 2012, 7 in 2013 and 1 in 2014. The mean age at death was 23.5 years (Table). Those who died were older and less likely to be on cART at the end of study-followup and had persistently lower CD4 counts and higher viral loads. The groups did not differ by sex, race/ethnicity, route of HIV acquisition, or BMI z-scores. Causes of death were derived from autopsy reports (3), study site records (12), family/friends report (6), primary HIV care provider (6) and obituary (1). Causes of death were wasting/multi-organ system failure/end stage AIDS (5), pneumonia (5), PML (4), PCP (2), disseminated MAI (2), B-cell lymphoma (2), suicide (2), sepsis (1), HIV-related cardiomyopathy (1), homicide (1) motor vehicle accident (1), hepatic failure (1), and tuberculosis meningitis (1).

Table Characteristics at last chart abstraction according to death status

Characteristics at Last Chart Review or Death		Status: Alive (N=1173)	Status: Died (N=28)	P-value
Sex (Male)		569 (48%)	9 (32%)	0.09
Perinatal HIV Transmission		1015 (87%)	25 (89%)	0.71
Age (in Years), Mean (SD)		20.6 (5.34)	23.5 (3.30)	0.005
Years on Study, Median (IQR)		3.61 (2.67, 4.21)	2.30 (1.16, 3.04)	<0.001
Race/Ethnicity[1]	White non-Hispanic	133 (11.4%)	3 (10.7%)	0.98
	Black non-Hispanic	681 (58.3%)	17 (60.7%)	
	Hispanic	324 (27.7%)	7 (25.0%)	
BMI z-score, Mean (SD)		0.40 (1.1)	-0.01 (1.8)	0.43
CD4 Count[2] (cells/μL), Mean (SD)		670 (1792)	168 (299)	<0.001
Percent of CD4 counts<200/μL during follow-up, Mean (SD)		10.7 (26.3)	70.7 (43.1)	<0.001
HIV RNA≥ 10,000 copies/mL		202 (17%)	18 (64%)	<0.001
Percent of HIV RNA>1000 copies/mL during follow-up, Mean (SD)		29.8 (32.8)	75.1 (28.4)	<0.001
Most Recent ARV Regimen[2]	cART	1010 (86%)	19 (68%)	0.01
	Non-cART ARV	94 (8.0%)	7 (25%)	
	Not on ARV	58 (4.9%)	2 (7.1%)	

SD=standard deviation; IQR=interquartile range; ARV=antiretroviral; BMI=body mass index; cART=combination ARV therapy (3 or more drugs from 2 or more classes). Age & BMI score are the last available measures during study follow-up.
[1] 31 reported other race or more than one race & 5 did not report race, [2] 2 missing CD4 counts, 11 missing most recent ARV regimen.

Conclusions: Deaths are uncommon among HIV-infected youth in the cART era, but infectious and non-infectious fatalities continue to occur, and most are HIV related. Deaths are more common among older youth, those not on cART, those with persistently lower CD4 counts, and those with higher HIV viral loads.

918 Transition to Adult Units: Situation and Evolution of Vertically HIV Infected Youths in Spain

Talía Sainz[1]; Carolina Fernández McPhee[2]; Santiago Jimenez de Ory[1]; Maria Isabel Gonzalez-Tome[3]; Rafael Rubio[3]; Jose I Bernardino[4]; Santiago Moreno[2]; Jose Antonio Iribarren[5]; Belen Alejos[6]; Marisa Navarro[7]
On behalf of the Spanish Cohort of AIDS Research (CORIS) and the Pediatric Spanish Cohort of HIV-infected Children (CoRISpe)
[1]Hospital Universitario Gregorio Marañón, Madrid, Spain; [2]Hospital Universitario Ramon y Cajal, Madrid, Spain; [3]12 de Octubre Hospital, Madrid, Spain; [4]La Paz University Hospital, Madrid, Spain; [5]Hospital de Donostia, San Sebastian, Spain; [6]Centro Nacional de Epidemiología, ISCIII, Madrid, Spain; [7]Hospital Gregorio Marañon, Madrid, Spain

Background: Due to the success of ART, many vertically HIV-infected youths (VHY) are being transferred to adult units. Our objective was to evaluate the transition process within the Spanish Cohort of vertically HIV infected children (CoRISpe), and to address the clinical situation of VHY in comparison to their horizontally HIV-infected peers (HHY)

Methods: Cross-sectional analysis including patients from 16 Hospitals, transferred to adult units between 1997 and 2012. Variables were analyzed before and one year after transition, and during follow-up (until December 2013). The cohort was compared to a cohort of HHY youths, on ART for at least one year.

Results: A total of 182 VHY were transferred during the study period, 58.2% female. Median age at transition was 17.9 years [17-19]. Patients transferred between 2009-2012 showed better immunological situation compared to their peers transferred before; CD4 757 cells/mm^3[559-932] *vs* 525[333-790], p<0.01, on viral suppression 62% *vs* 30.9%, p<0.01. Longitudinal data were available for 147 patients (4 died after transition, 6 had changed to non-participating hospitals, and 18 never showed up at adult units and are lost to follow up). From 81 virologically suppressed patients, 86.4% maintained suppression after transition, whereas in 13.6% HIV RNA became detectable. A 69.9% of patients transferred with CV>50cop/mL, achieved viral suppression after transition. No association was found between evolution and gender or age at transition, and none of the studied factors was associated with loss of viral suppression. Compared to the 46 HHI (61% heterosexual, 35% MSM), VHY were younger (24±3.7 *vs* 26.5±3.1, p<0.01) and 58% *vs* 57% were female (p=ns). Despite the fact that 27% *vs* 6.5% were on CDC stage C (p<0.01) and had lower CD4 nadir (202[78-364] *vs* 286[170-370], p=0.17), their CD4 T-cell count was higher (744[IQR 505-990] *vs* 542[391-662], p<0.01, %CD4 33[24-39] *vs* 27[22-34] p<0.01 and CV<50 cop/mL : 80% *vs* 73%, p=0.41. On NNRTI: 27% vs 50% (p=0.04) and 74% vs 83% (p=0.41) were on a once daily regimen.

Conclusions: Compared to previous years, the immunological situation of VHY transferred today is much better, and remains stable or improves after transition in 75% of patients. Despite many years of infection, their immunological situation is comparable to that of their horizontally infected peers. However, strategies are needed in order to increase engagement in care during transition.

WEDNESDAY, FEBRUARY 25, 2015

Session P-U4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Treatment and Monitoring Strategies in Children

919 Long-Term Consequences of Planned Treatment Interruption in HIV-1–Infected Children

Riccardo Freguja[1]; Hahhah Poulson[2]; Paola Del Bianco[3]; Alexandra Compagnucci[4]; Yacine Saidi[4]; Carlo Giaquinto[5]; Lynda Harper[6]; Diana M. Gibb[6]; Nigel J. Klein[2]; Anita De Rossi[1]
[1]1 AIDS Reference Center, Section of Oncology and Immunology, Padova, Italy; [2]Institute of Child Health, London, United Kingdom; [3]Istituto Oncologico Veneto-IRCCS, Padova, Italy; [4]Inserm SC10, Paris, France; [5]Department of Mother and Child Health, Padova, Italy; [6]Medical Research Council, London, United Kingdom

Background: The planned antiretroviral treatment interruption (PTI) in children with HIV infection is associated with rapid immunological and virological changes compared to children on continuous therapy (CT) (PENTA 11 trial; Plos One 2013, 10:e76582). After the end of PENTA 11 trial all children were advised to resume ART. The long-term immunological and virological outcomes were evaluated in children for up to 4 years after end of the trial by randomized arm.

Methods: 54 children (randomized at main trial baseline: 23 to CT and 31 to PTI arm) entered the long-term substudy. Immunophenotyping of CD4 and CD8 memory and naive cell subsets, thymic output by means of TREC quantification, cell-associated HIV-DNA and HIV-RNA were analysed on available samples at 1, 2, 3, and 4 years after the end of the trial.

Results: The median baseline age was 9.0 years and median follow-up was 6.1 years. At 1 year follow-up, levels of cell-associated HIV-DNA were higher in PTI than in CT children (295 vs 70 copies/10*6cells; p=0.035) as were the proportion of children with detectable HIV-RNA in plasma (35% vs 6%; p=0.046). Mean [95% CI] CD4 cells were lower in PTI than CT (708[578-837] vs 876 [738-1014] cells/mm^3; p=0.082) as were the percentage of CD4 memory cells out of the total lymphocytes (12.6[9.8-15.4] vs 19.3[15.7-22.9]; p=0.0045). CD4 naive cells did not significantly differ between the two groups (21.3[17.5-25.2] vs 19.0[14.1-24.0]), and TREC levels were higher in PTI arm (2551[2049-3054] vs 1855[1283-2428] copies/10*5cells; p=0.073). CD8 cells tended to be higher in PTI than CT (37.7[33.8-41.5] vs 33.0[28.8-37.2]; p=0.110). At 2, 3 and 4 year follow-up, none of the above parameters significantly differed between PTI and CT, except for the percentage of CD4 memory cells which continued to be lower in PTI than CT at 4 years follow-up (14.8[12.0-17.5] vs 21.0[17.5-24.6]; p=0.0064). Cell-associated HIV-RNA was higher in PTI than CT children (3.01 vs 2.70 $\log_{10}$ copies/10*6 cells), consistent with a higher level of productive infection in the former.

Conclusions: Most of the short term immunological and virological consequences of PTI were still present 1 year after the end of the trial, but no longer detectable after 2 years follow-up. Interestingly, CD4 memory cells continued to be lower in PTI children. While thymic output may compensate for loss of naive CD4 cells, the persistent depletion of CD4 memory cells may result from higher residual productive infection in PTI than in CT children.

920 Can CD4 Monitoring in Virologically Suppressed Children be Reduced or Stopped?

Mary-Ann Davies[1]; Helena Rabie[2]; Geoff Fatti[3]; Kathryn Stinson[1]; **Karl-Günter Technau**[4]; Shobna Sawry[5]; Brian Eley[6]; Lynne Mofenson[7]; Andrew Boulle[1]; IeDEA Southern Africa[8]
[1]University of Cape Town, Cape Town, South Africa; [2]University of Stellenbosch, Cape Town, South Africa; [3]Kheth'Impilo, Cape Town, South Africa; [4]University of the Witwatersrand, Johannesburg, South Africa; [5]University of Witwatersrand, Johannesburg, South Africa; [6]University of Cape Town, Cape Town, South Africa; [7]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US; [8]Univeristy of Cape Town and University of Bern, Cape Town, South Africa

Background: Although studies suggest CD4 monitoring can be reduced in adults on antiretroviral therapy (ART) with viral suppression after initial CD4 recovery, there are limited data in children, particularly in resource-limited settings. We evaluated probability of CD4 decline in children with viral suppression and CD4 recovery after 1 yr on ART in southern Africa.

Methods: Children initiating ART at IeDEA-SA sites with routine HIV-RNA monitoring were included if:

(1) they were "responders"(HIV-RNA <400 copies/ml and no severe immunosuppression after ≥1 yr on ART [time 0]) AND (2) ≥1 HIV-RNA and CD4 measurement within 15 mos of time 0. Outcome was CD4 decline to below WHO-defined thresholds for severe immunosuppression (CD4<20%/750 cells/mm^3 if age 12-35 mos, CD4 <15%/350 cells/mm^3 if age 36-59 mos, CD4 <15%/200 cells/mm^3 if age ≥5 yrs). We determined the probability of the outcome during the 3 yrs after time 0 if viral suppression was maintained, censoring follow-up at the first of (1) day before first HIV-RNA measurement >400 copies/ml (2) day before a >15 mo gap in testing or (3) end of follow-up due to death, loss to follow-up (LTFU), transfer out or database closure. Associations between characteristics at time 0 and CD4 decline were examined using Cox-proportional hazards models.

Results: 5984 children met the inclusion criteria; most were ≥2 years old at time 0 with no/mild immunosuppression and on ART for <18 mos. The probability of a CD4 decline to severe immunosuppression was <3% (Table). Risk of CD4 decline was higher in children age <2 yrs (Adjusted Hazard Ratio [aHR]:3.40 [95%CI: 2.52-4.57]), those with moderate vs no/mild immunosuppression (aHR:3.29 [2.57-4.21]) and duration on ART ≥18 mos (aHR:1.68 [1.28-2.21]). A subsequent CD4 measurement was available in 169 of 270 (62%) children with after initial CD4 decline. The decline was transient in 86%, with recovery at next measurement. Among 270 children with a CD4 decline, outcomes in the following yr were: 85.2% in care, 1.1% died, 1.9% LTFU and 11.9% transferred out.

Table: Characteristics at time 0 and probability (95% CI) of CD4 decline within 3 yrs. No/mild immunosuppression defined as CD4 ≥25%/1000 cells/mm^3 (age <5 yrs) or ≥20%/500 cells/mm3 (age ≥5 yrs).

ART duration at time 0	<18 months		≥18 months	
	no/mild immunosuppression	moderate immunosuppression	no/mild immunosuppression	moderate immunosuppression
Age <2years	n=522 9.4% (6.5-13.4)	n=159 19.9% (13.8-28.1)	n=30 26.4% (8.4–65.8)	n=6 37.5% (10.7-85.8)
Age ≥2years	n=2,368 2.8% (2.1-3.8)	n=1,412 9.0% (7.2-11.1)	n=967 4.2% (2.8-6.4)	n=520 13.9% (10.3-18.7)

Table: Characteristics at time 0 and probability (95% CI) of CD4 decline within 3 yrs. No/mild immunosuppression defined as CD4 ≥25%/1000 cells/mm^3 (age <5 yrs) or ≥20%/500 cells/mm3 (age ≥5 yrs).

Conclusions: These results suggest that CD4 monitoring could be reduced or stopped in children >2 yrs with viral suppression who attain CD4 indicating no/mild immunosuppression within 18 mos of starting ART.

TUESDAY, FEBRUARY 24, 2015

Session P-U5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Determinants of Disease Progression in Children

921 Impact of Sex Differences on Disease Outcome in Pediatric HIV in South Africa

Masahiko Mori[1]; Emily Adland[1]; Alice Swordy[1]; Maximilian Muenchhoff[1]; Nora Lavandier[1]; Jacob Hurst[1]; Thumbi Ndung'u[2]; Andy Prendergast[3]; Philip J. Goulder[1]; Pieter Jooste[4]

[1]University of Oxford, Oxford, United Kingdom; [2]University of KwaZulu-Natal, Durban, South Africa; [3]Queen Mary University of London, London, United Kingdom; [4]Kimberley Hospital, Durban, South Africa

Background: To identify sex differences in CD4 count and viral load in antiretroviral therapy (ART)-naïve children, and in ART initiation and post-treatment outcome among ART-treated HIV-infected children.

Methods: We studied 2168 South African HIV-infected children, of whom 1819 initiated ART. Statistical analyses were performed to identify sex differences in HIV disease outcome measures, including pre-ART CD4 and viral load; ART initiation; and post-ART immune reconstitution and mortality.

Results: Absolute CD4+ count and CD4% were higher in ART-naïve female compared to age-matched male HIV-infected children. CD4 count and CD4% were also significantly higher in female versus male HIV-uninfected neonates. Compared with children in whom ART was initiated (47% female), children who did not meet criteria to start ART by ≥5yrs were more frequently females (59%; p<0.0001). Among ART-treated children, there was no significant sex difference in mortality post-ART. However, immune reconstitution of CD4 T-cells to the levels of age-matched uninfected controls was more rapid and more complete in female children (Figure). Whereas ART was initiated as a result of meeting CD4 criteria less often in females (45%), ART initiation above CD4 thresholds, due to meeting clinical criteria, occurred more often in females (58%, p=0.0005).

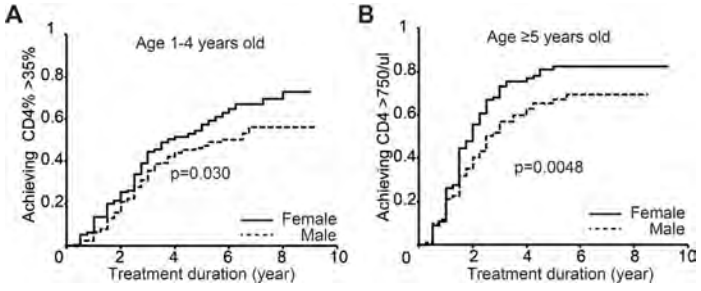


Figure. Sex differences Immune reconstitution amongst the patients who started treatment under the pre-2013 WHO guidelines. Sex differences by log rank test are shown as follows: A. CD4+ T cell percentage recovery (>35%) rate among the children who started ART aged 1-4 years old with CD4+ T cell <25%. B. Absolute CD4+ T cell count recovery (>750/ul) among children initiating ART aged ≥5 years old with CD4+ T cell counts <350/ul.

Conclusions: Significant sex differences are evident in disease outcome in HIV-infected children. These data suggest that, in females, CD4 counts are intrinsically higher from birth, resulting in delayed ART initiation and increased morbidity. These findings are of relevance in considering optimal ART use in HIV-infected children.

922 CD31 Expression on CD4 Cells Predicts Clinical Course of HIV in a Perinatally HIV-Infected Cohort

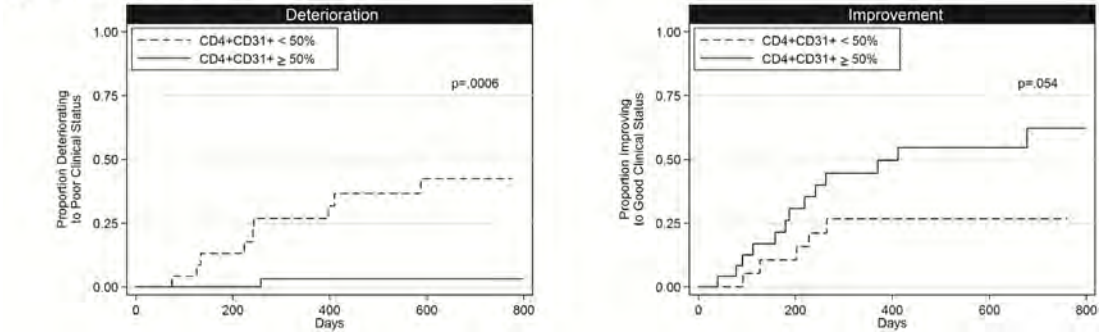
Ramia Zakhour[1]; Gilhen Rodriguez[2]; Cynthia Bell[2]; Guenet Degaffe[2]; Laura Benjamins[2]; Gabriela DelBianco[2]; Elizabeth Donnachie[2]; Tran Dat[2]; Gloria P. Heresi[2]; James R. Murphy[2]
[1]University of Texas, Houston, TX, US; [2]UTHealth Medical School, Houston, TX, US

Background: Thymic production of T-cells is important for maintenance of good immunological function in HIV infected individuals, however methods of measurement of recent thymus emigrant (RTE) T-cells are not easily adapted to use in HIV clinics. CD31 expression on CD4 cells is a marker of RTE CD4 cells and can be easily incorporated into common clinical monitoring procedures. We hypothesized that quantification of RTE measured as CD4+CD31+ predicts subsequent clinical course of HIV infection.

Methods: We performed a 2 year longitudinal prospective study of 69 perinatally HIV infected individuals from a single HIV clinic. CD31 expression was measured using a modified FACS procedure incorporating a FITC-conjugated anti CD31 (MBC78.2) into a standard CD4+ measurement routine. Other data are from medical records. For analyses, patients' HIV clinical status was categorized as good (CD4 ≥ 25% and HIV RNA ≤ 50 copies/ml), intermediate (≥25%, > 50) or poor (< 25%, >50). Spearman's rho, Kruskal-Wallis, Kaplan-Meier, Log Rank tests and Cox proportional hazards models were used.

Results: CD4+CD31+ cells correlated positively with CD4+ numbers but were independent of plasma HIV RNA level. Using an experiment determined discriminator of 50% CD4+CD31+, we used Kaplan-Meier analyses to test whether baseline CD4+CD31+ value predicts subsequent clinical status. Patients in good or intermediate clinical status who had CD4+CD31+ values < 50% at enrollment had significant (p 0.0006) deterioration to the clinically poor classification over the subsequent 2 years as compared to those with CD4+CD31+ ≥ 50% (Figure). Reciprocally, patients in poor or intermediate clinical status who had CD4+CD31+ ≥ 50% at enrollment had significant improvement to clinically good status (p 0.054) over 2 years as compared to those with CD4+CD31+ < 50%. CD4+CD31+ measurements provided a predictive capacity that did not overlap with T-cell activation measured as CD8+CD38+ >17%.

Figure 1. Change in Clinical Status



CD31 on CD4+ cells is a practical addition to established routine methods for immunological assessment of HIV patients and is applicable even with rudimentary FACS hardware.

Conclusions: For perinatally HIV infected patients in good immunological status, the finding of < 50% of CD4 cells expressing CD31 is a predictor of subsequent clinical deterioration. The population identified by this CD31-based criterion did not overlap with that classified as having poor prognosis using the CD8+CD38+ marker of T-cell activation.

923 Premature Aging and Immune Senescence in HIV-1-Infected Children

Ketty Gianesin[1]; Antoni Noguera-Julian[2]; Marisa Zanchetta[3]; Osvalda Rampon[1]; Clàudia Fortuny[2]; Mireia Camós[2]; Carlo Giaquinto[1]; Anita De Rossi[1]
[1]University of Padova, Padova, Italy; [2]Hospital Sant Joan de Déu-Universitat de Barcelona, Barcelona, Spain; [3]Istituto Oncologico Veneto–IRCCS, Padova, Italy

Background: Several data indicate that HIV-1-infected adults undergo premature aging and immune senescence; chronic immune activation may play a critical role in these dysfunctions. Limited data are available for HIV-1-infected children, in whom immune activation and senescence are likely to be more deleterious, since their immune system co-evolves from birth with HIV-1.

Methods: 71 HIV-1-infected (HIV^+) children, aged from 0-5 years, 65 HIV-1-exposed-uninfected (HEU) and 49 HIV-1-unexposed-uninfected (HUU) age-matched children were studied. 41% of the HIV^+ children were not on antiretroviral therapy (ART). Telomere length (TL) and T-cell receptor rearrangement excision circle (TREC) levels were quantified in peripheral blood cells by Real-Time PCR. Subgroups of 18 HIV^+, 21 HEU and 19 HUU children were studied for CD4 and CD8 cell differentiation (CD45RA,CD27), senescence (CD28,CD57) and activation/exhaustion (CD38,HLA-DR,PD1) markers by flow cytometry. Statistical analyses were performed with SPSSv21.

Results: TL were significantly shorter in HIV^+ than in HEU and HUU children (overall p=0.009, adjusted for age); moreover, HIV^+ ART-naïve children had shorter TL compared with children on ART (median 2.1[interquartile range 1.7-2.4] *vs* 2.6[2.0-3.0]; p=0.002). CD8 naïve cells ($CD45RA^+CD27^+$) and TREC levels were significantly lower in HIV^+ than in HEU and HUU groups (overall, p<0.001 and p<0.001, respectively), while percentages of CD8 effector memory ($CD45RA^-CD27^-$) and terminally differentiated cells ($CD45RA^+CD27^-$) were higher in the former (overall, p=0.025, and p<0.001, respectively). CD8 senescent cells ($CD57^+CD28^-$) were higher in HIV^+ than in HEU and HUU children (33.0[17.8-50.0] *vs* 10.6[3.4-36.2] *vs* 11.8[5.9-22.6]; p=0.002) as were CD8 activated cells ($HLA\text{-}DR^+CD38^+$) (7.9[4.1-17.2] vs 4.7[3.9-7.7] vs 3.4[2.8-7.6]; p=0.09). PD1 expression on CD8 cells was higher in HIV^+ children than in HEU and HUU groups (overall, p<0.001) and strongly related to CD8 activated cells (r=0.806, p<0.001). Within CD4 cell subset, percentages of activated and senescent cells did not differ between HIV^+ and controls, although PD1 expression tended to be up-regulated in HIV^+ children (overall, p=0.094).

Conclusions: HIV-1-infected children exhibit a premature biological aging with accelerated immune senescence which affects the CD8 cell subset in particular. HIV-1 infection *per se* seems to influence the aging process, rather than exposure to ART for prophylaxis or treatment.

924 *KIR/HLA* Alleles Alter $CD4^+$ Lymphocyte Count and Viral Load in HIV-Infected Children

Kumud Singh[1]; Min Qin[2]; Sean Brummel[2]; Konstantia Angelidou[2]; Rodney Trout[1]; Terrence Fenton[2]; Stephen Spector[1]
[1]University of California San Diego, La Jolla, CA, US; [2]Harvard School of Public Health, Boston, MA, US

Background: HLA class I molecules are ligands for killer cell immunoglobin like receptors (KIR) that affect innate and adaptive immunity, and are of importance in controlling the antiviral response of NK cells. Despite their significance in the immune response, effects of KIR/HLA on HIV disease of children have not been previously studied. We hypothesized that the interactions of *KIR* and *HLA* alleles would affect HIV pathogenesis in children.

Methods: 993 antiretroviral naïve children with symptomatic HIV infection from PACTG protocols P152 and P300 were genotyped for *KIR* and *HLA* alleles using Luminex platform. Linear regression with a robust variance estimator was used to test association between genotypes and baseline HIV RNA, $CD4^+$ count, and cognitive score, adjusting for age, race/ethnicity and study. Because the role of innate and adaptive immunity can differ by age, interaction between genetic markers and age group ≤2 years (n=460) and ≥2 years

(n=533)) was investigated. For genetic markers with marginally significant association by age interaction (p<0.1), linear regression models were fit to each age group separately. False discovery rate (FDR) was used to adjust for multiple testing.

Results: Children with the *KIR2DS4*ALL FULL LENGTH* (*KIR2DS4*AFL*) allele had higher CD4$^+$ counts vs. those without it (+265 cells; p=0.001). Consistent with these CD4$^+$ findings, children 0-2 years with *KIR2DS4*AFL* had lower plasma HIV RNA (-0.57log10 copies/ml; p=0.006) and those with *KIR2DS4*AFLEX5* had higher cognitive index scores (+5.34; p=0.004). Children 2-18 years with *KIR3DS1+Bw4-801* had higher plasma HIV RNA (+0.36log10; p=0.001). These results remained significant after controlling for multiple testing. Other *KIR* and *KIR/HLA* alleles with significant associations in univariate analyses, but not after controlling for FDR included: higher HIV RNA in children with *KIR2DS2* (0.17log10; p=0.035); higher CD4$^+$ counts in children with *KIR3DL1+Bw4* (+204 cells: p=0.006); higher cognitive index scores in children with *KIR2DL2*001/2/3/5* (+4.6; p=0.01) and lower cognitive index score with *KIR2DL5* in children 2-18 years (-2.95; p=0.038).

Conclusions: These data show for the first time that specific *KIR* alleles independently or combined with HLA ligands affect HIV viral load, CD4$^+$ counts and cognitive index scores of infected, antiretroviral naive children, and these effects appear to be age dependent. These data support a role for specific *KIR* alleles in HIV pathogenesis.

THURSDAY, FEBRUARY 26, 2015

Session P-U6 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Complications of HIV and ART: Pulmonary and Cardiovascular Outcomes

925 Arterial Stiffness in HIV+ Youth and Associations With HIV-Related Variables

Allison R. Eckard[1]; Julia C. Rosebush[1]; Mary Ann O'Riordan[2]; Christopher T. Longenecker[2]; Bridget Wynn[1]; Monika Uribe Leitz[1]; Danielle Labbato[2]; Norma Storer[2]; Bruce Kinley[2]; Grace A. McComsey[2]

[1]Emory University School of Medicine, Atlanta, GA, US; [2]Case Western Reserve University, Cleveland, OH, US

Background: Several studies show that HIV+ youth are at an increased cardiovascular disease (CVD) risk as assessed by carotid intima-media thickness (cIMT). Pulse wave velocity (PWV) measures arterial stiffness and is another surrogate measure of CVD risk. Few data exist on PWV in HIV+ youth.

Methods: HIV+ youth 8-25 years old on stable ART with an HIV-1 RNA level <1000 copies/mL were prospectively enrolled, along with a group of healthy controls similar in age, sex and race. Carotid-femoral PWV was assessed in triplicate with the SphygmoCor system at a single study visit and averaged (higher PWV = increased arterial stiffness). cIMT, fasting lipids, insulin resistance and CD4 were also measured. We used non-parametric tests and Spearman coefficients to assess differences between groups and correlations with PWV, respectively. Multivariable regression analysis was performed to determine variables independently associated with PWV.

Results: 101 HIV+ youth and 86 healthy controls were included. Groups were similar in age, sex and race (HIV+: median (IQR) age = 19 (14, 23) years, 64% male, 89% black). HIV+ group had a median (IQR) HIV & ARV duration of 8 (2, 15) and 3 (1, 10) years, respectively, with a CD4 count of 652 (449, 872) cells/mm^3. Median (IQR) PWV for the HIV+ group was 5.7 (5.1, 6.2) m/s vs. 5.7 (4.9, 6.5) m/s in controls (P=0.81). In the HIV+ group, PWV was positively correlated with systolic & diastolic blood pressure (BP) (both R=0.3; P<0.01), mean bulb & internal carotid artery IMT (both R=0.3; P≤0.02), male sex (P=0.01), current alcohol use (P<0.01), detectable HIV-1 RNA (P=0.03) and current tenofovir use (P<0.01), and negatively correlated with CD4 count & ARV duration (both R=-0.2; P≤0.04). In the controls, PWV was positively associated with BP (systolic R=0.2; P=0.04; diastolic R=0.3; P<0.01), age (R=0.5; P<0.01), body mass index (BMI) (R=0.4; P<0.01), and current smoking, marijuana and alcohol use (P≤0.04). In multivariable regression, only current alcohol use was independently associated with PWV (P<0.01) in the HIV+ group, whereas, age and BMI were associated with PWV (both P≤0.03) in the controls.

Conclusions: This is the largest study of PWV in HIV+ youth to date. There was no difference in PWV between the HIV+ youth and healthy controls. PWV, however, was positively correlated with cIMT in the HIV+ youth, which supports the use of PWV as a measure of CVD risk in this population. Current alcohol use was associated with arterial stiffness, which deserves further investigation.

926 Does Early ART Normalize Pulse-Wave Velocity in Children? Evidence From CHER Cohort

Steve Innes[1]; Zukiswa Magogotya[1]; Philip Herbst[1]; Mark F. Cotton[1]; Barbara Laughton[1]; Sara Browne[2]; Richard Haubrich[2]

[1]Stellenbosch University, Cape Town, South Africa; [2]University of California San Diego, San Deigo, CA, US

Background: Non-communicable diseases such as atherosclerosis are becoming more important as many HIV+ children on ART are reaching school age. Cross-sectional evidence suggests increased prevalence of vascular disease in children on ART after adjustment for traditional atherosclerosis risk factors. This is associated both with advanced HIV disease and with ART itself (particularly lopinavir/ritonavir, LPVr). Aorto-femoral pulse wave velocity (PWV), a measure of arterial elasticity, predicts incident cardiovascular events in asymptomatic adults and is a gold-standard marker of subclinical atherosclerosis. Previous studies in children have focussed on children initiating ART much later than 3 months of age. Our aim was to measure PWV in school children who initiated LPVr-based ART before 3 months of age.

Methods: Cross-sectional PWV and fasted lipid measurements on primary-school-age children who initiated LPVr-based ART in the CHER trial by 3 months of age, with an existing HIV-uninfected control group from the same communities and socio-economic background. Multivariate linear regression to determine the association between PWV and HIV infection.

Results: See table. Unadjusted PWV and growth parameters were similar in the 2 groups. After adjustment for age, gender and body-mass-index-for-age z-score, HIV+ children had adjusted mean total cholesterol 0.7 mmol/L higher than controls (p<0.0001), adjusted mean LDL cholesterol 0.5 mmol/L higher (p=0.001), adjusted mean triglycerides 0.4 mmol/L higher (p<0.0001) and adjusted mean triglyceride to HDL cholesterol ratio 0.3 higher (p<0.0001). However, HIV infection was not associated with differences in PWV after adjustment for age, gender, and systolic blood pressure (p=0.40), despite 80% power to detect a difference as small as 0.3 meters/second.

Table 1: Demographics, clinical characteristics and pulse-wave velocity. Variables are presented as median (interquartile range).

	HIV-infected	Uninfected controls	Unadjusted p-value (two-tailed)
n	59	43	
Age at study visit (years)	7.7 (7.6 – 7.8)	8.5 (7.8 – 8.7)	<0.0001
Gender (male/female)	46% / 54%	77% / 23%	<0.0001
Age at ART initiation (***weeks***)	8 (7 – 10)		
Cumulative time on ART (years)	7.1 (6.6 – 7.5)		
Dominant ART regimen (ZDV / 3TC / LPVr)	84% / 93% / 93%		
Cumulative time with undetectable HIV RNA PCR viral load (<400 copies/ml) (months)	28 (19 – 44)		
Proportion with undetectable HIV RNA PCR viral load (<400 copies/ml) at study visit	91%		
Nadir CD4%	21% (16 – 25%)		
Nadir CD4 (cells/mm^3)	705 (576 – 871)		
Cumulative time with low CD4 or CD4% § (months)	4 (0 – 14)		
Current CD4 (cells/mm^3)	1072 (826 – 1427)		
Maximum WHO clinical stage (1 or 2 / 3 / 4)	10% / 44% / 46%		
Weight-for-age Z-score	-0.4 (-1.0 – 0.3)	-0.2 (-1.0 – 0.8)	0.42
Height-for-age Z-score	-0.8 (-1.3 – 0.1)	-0.4 (-1.4 – 0.3)	0.24
Body mass index-for-age Z-score	0.0 (-0.5 – 0.7)	0.0 (-0.6 – 1.1)	0.77
Waist circumference to height ratio	0.5 (0.4 – 0.5)	0.4 (0.4 – 0.5)	0.17
Systolic blood pressure (mmHg)	96 (88 – 100)	96 (92 – 103)	0.05
Total cholesterol (mmol/L)	4.3 (3.7 – 4.9)	3.5 (3.1 – 4.0)	<0.0001
Triglycerides (mmol/L)	0.8 (0.7 – 1.2)	0.6 (0.4 – 0.7)	<0.0001
HDL cholesterol (mmol/L)	1.2 (1.1 – 1.4)	1.3 (1.1 – 1.5)	0.57
Triglyceride to HDL cholesterol ratio	0.7 (0.5 – 1.0)	0.4 (0.3 – 0.6)	<0.0001
LDL cholesterol (mmol/L)	2.6 (2.0 – 3.2)	1.9 (1.4 – 2.4)	<0.0001
Glycosylated hemoglobin (%)	5.4% (5.2 – 5.7%)	5.8% (5.6 – 6.0%)	0.16
Pulse-wave velocity (meters/sec)	4.8 (4.4 – 4.9)	4.9 (4.4 – 5.2)	0.20

ZDV=zidovudine. 3TC=lamivudine. LPVr=lopinavir/ritonavir.

§ Low CD4 or CD4% was defined as CD4<1000 or CD4%<25% for <12 months of age; CD4 <750 or CD4% <20% for 12-35months of age; CD4 <500 or CD4% <20% for >36months of age.

Table 1: Demographics, clinical characteristics and pulse-wave velocity.

Conclusions: Despite significantly elevated lipids and prolonged LPVr-based ART exposure, arterial elasticity was no different in HIV+ school-age children and uninfected controls. Early ART may prevent early HIV-related inflammatory vascular damage.

927 The Impact of HIV and ART on Markers of Inflammation, Vascular Injury and Disordered Thrombogenesis in Children

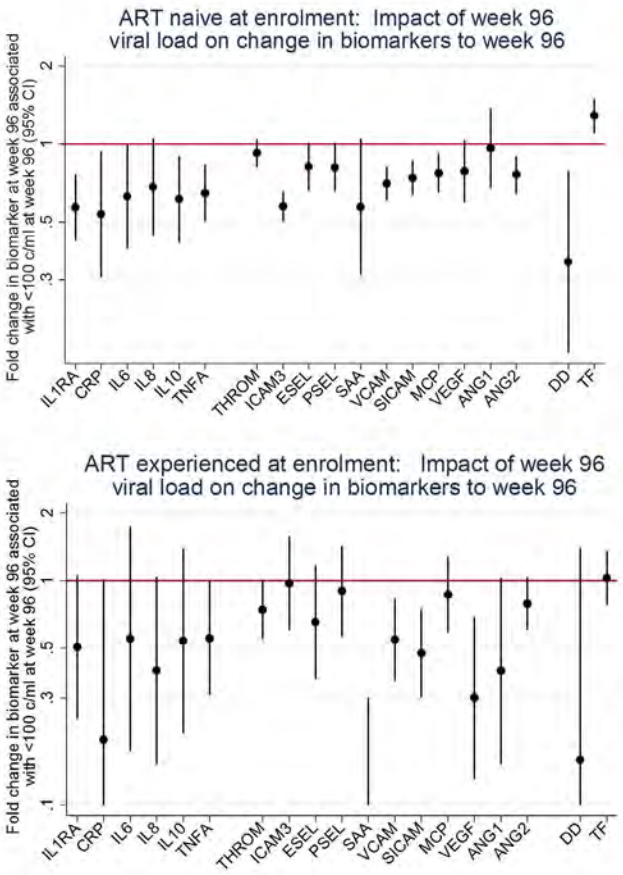
Julia M. Kenny[1]; Sarah Walker[1]; Adrian Cook[1]; Victor Musiime[2]; Priscilla Wavamunno[2]; Florence Odongo[2]; Grace Mirembe[2]; Dorica Masaku[3]; Diana M. Gibb[1]; Nigel J. Klein[1]

[1]University College London, London, United Kingdom; [2]Joint Clinical Resarch Centre, Kampala, Uganda; [3]University Teaching Hospital, Lusaka, Zambia

Background: Markers of inflammation are generally increased in HIV-infected individuals. However, few data are available from young African children and longitudinal data are sparse.

Methods: ART naïve and ART experienced (on d4T+3TC+NNRTI for >2 years, virologically suppressed) children from the CHAPAS-3 trial in Uganda/Zambia were included, with age-matched controls. A panel of biomarkers to measure inflammation (IL1Ra, high sensitivity CRP, IL6, IL8, IL10 and TNFa), vascular injury (thrombomodulin(TM), E-selectin, P-selectin, serum amyloid A (SAA), VCAM1, ICAM1, MCP1, VEGF and angiopoietin(Ang) 1+2) and disordered thrombogeneis (d-dimers, soluble tissue factor(TF)) were measured at baseline in all children and repeated at 48 and 96 weeks in the HIV-infected children. Associations between change in log10 biomarkers from week 0 to 96 and baseline VL and age, and VL suppression at week 96, were estimated using normal linear regression.

Results: 208 HIV infected ART naïve, 74 HIV infected ART experienced and 284 HIV uninfected controls were recruited. At baseline 13/19 biomarkers were significantly ($p<0.05$) higher in the ART naïve vs controls, ART experienced vs controls and ART naïve vs ART experienced. TM and TF levels were similar in ART naïve and controls. In the experienced group, after a mean 3.7 years on ART baseline levels of IL1Ra, SAA and sICAM were comparable to controls. Baseline Ang-1 levels were similar in ART naïve and experienced children but higher than controls. By week 96, all biomarkers had significantly declined excepting SAA, Ang-1 and 2 in the ART naïve group and P-selectin in the ART experienced group. In naïve children, the only biomarkers for which declines to week 96 were not greater in children with VL<100 c/ml at week 96 compared to those >100 c/ml were TM, Ang-1 and TF ($p>0.1$) (Figure). For IL10, TNFa, MCP, SAA, VCAM, VEGF, Ang-2 declines to week 96 were independently greater in older children ($p<0.1$). Fewer biomarker declines were associated with week 96 VL<100 c/ml in experienced children. There was no independent effect of baseline VL on week 96 declines in any biomarker ($p>0.1$).



Conclusions: All biomarkers tended to start high and showed ongoing normalization with progressive treatment, even in experienced children already on ART for ~4 years. Of particular interest, the improvement in vascular biomarkers with treatment is compatible with the beneficial effects of ART on markers of cardiovascular structure and function in this cohort.

928 T-Cell Activation and E-Selectin Associated With Coronary Plaque in HIV-Infected Youth

Julia B. Purdy; Aylin Unsal; Khaled Abd-Elmoniem; Adam Rupert; Joseph A. Kovacs; Rohan Hazra; Ahmed Gharib; Colleen Hadigan

National Institutes of Health, Bethesda, MD, US

Background: Adolescents and young adults (AYA) infected with HIV early in life may be at increased risk of atherosclerotic cardiovascular disease (CVD). Chronic inflammation and circulating adhesion molecules may play a role in the early pathogenesis of atherosclerosis, however, the mechanism of vascular injury in this population is still unclear. The aim of this study was to measure biomarkers of cardiovascular injury and immune activation in relationship to coronary plaque burden in patients infected with HIV early in life.

Methods: 35 AYA who acquired HIV early in life and 11 healthy controls were examined in this prospective cross-sectional study. All participants were free of active CVD at the time of evaluation. CT angiography was utilized for coronary plaque quantification. Number of atherosclerotic plaques, calcified and non-calcified, was determined in each of the 17 American Heart Association coronary segments.

Results: We studied HIV+ subjects (mean age 22; 15-29 years; 54% male) and control subjects (mean age 25; 22-29 years; 27% male). No calcified plaque was found in either group. No significant difference in number of plaque lesions between groups (HIV+ median 0, range 0-4, Control median 0, range 0-7, p=0.08). Activated CD8 T cells in the periphery, as measured by %CD8+CD38+DR+, was associated with increased coronary plaque in the HIV+ group (Table 1). Levels of activated peripheral CD8 T-cells (%CD8+CD38+DR+, p =0.025) were significantly associated with coronary plaque in HIV, but not levels of activated CD4 T-cells (%CD4+CD38+DR+). E-selectin was significantly associated with plaque in HIV+ subjects (p=0.006). In a multivariate analysis only %CD8+CD38+DR+ was significant (Table 1). Although P-selectin, sICAM-3, VCAM-1, TIMP-1, and MCP-1 levels were significantly elevated in HIV, these biomarkers did not relate to plaque, nor did lipopolysaccharide binding protein.

Table 1. Univariate and Multivariate Associations of Coronary Plaque among HIV+ Subjects (n=35)

	Correlation Coefficient (r)	p-value	Multivariate Regression Model 1		Multivariate Regression Model 2	
			Estimate	p-value	Estimate	p-value
Age (y)	0.002	0.99	0.04	0.08	0.04	0.07
Smoking pack-years	0.08	0.7	0.08	0.77	-0.008	0.76
E-selectin (ng/mL)	0.48	**0.006**	0.005	0.76	0.003	0.84
CD8+CD38+DR+ (%)	0.46	**0.025**	0.012	**0.01**	0.0097	**0.04**
LDL Cholesterol (mg/dL)	0.78	**< 0.001**	--	--	0.002	0.51

Model 1 is a multivariate fit model including age, smoking pack-years, E-selectin, and current %CD8+CD38+DR+. **Model 2** adds LDL to Model 1.

Conclusions: Prior investigation in HIV+ adults identified an association between increased carotid lesions and T-cell activation markers. We identify a significant relationship between increased coronary plaque and levels of activated T-cells in AYA with life-long HIV. Further, soluble E-selectin, which has also been linked with carotid artery plaque and atherosclerosis, was positively correlated with coronary plaque in the present study. The presence of increased circulating adhesion molecules and markers of immune activation may be early predictors of atherosclerosis in AYA infected with HIV early in life.

929 High Prevalence of Dyslipidemia and Insulin Resistance in African Children on ART

Steve Innes[1]; Kameelah L. Abdullah[2]; Richard Haubrich[2]; Sara Browne[2]; Mark F. Cotton[1]

[1]*Stellenbosch University, Cape Town, South Africa;* [2]*University of California San Diego, San Deigo, CA, US*

Background: Antiretroviral therapy (ART)-induced dyslipidemia and insulin resistance in African children may be a major public health threat to an already vulnerable population. Data describing the true extent of dyslipidemia and insulin resistance in perinatally-infected children on ART in Africa is sparse.

Methods: Fasting total cholesterol, LDL, HDL, triglycerides, insulin and glucose were performed on the first 100, of 190 pediatric HIV clinic attendees on ART. Diet assessment was performed by a trained dietician. Lipoatrophy was formally graded by consensus between two expert HIV pediatricians. Durations of previous ART exposures, WHO clinical stage, pre-ART viral load, nadir and current CD4 were recorded. Dual energy X-ray Absorptiometry (DEXA) was performed on a subset of 42 patients selected semi-randomly.

Results: Prevalences of insulin resistance, abnormal total cholesterol, LDL, HDL and triglyceride were 10%, 13%, 12%, 13 % and 9% respectively. Overall, 40% had at least one lipid abnormality or insulin resistance. Adjusted mean LDL cholesterol increased by 0.24mmol/L for each additional year of cumulative lopinavir/r exposure (p=0.03) after adjusting for age, gender, body mass index, previous stavudine exposure, dietary fat and refined carbohydrate, while adjusted mean LDL cholesterol was 0.9mmol/L higher in children exposed to efavirenz within the previous six months (p=0.01). We found no significant difference in blood lipids or insulin resistance index in patients with and without visually obvious lipoatrophy (p>0.20), and no correlation with DEXA measures of peripheral fat maldistribution (p>0.15).

Multivariate Regression model of the predictors of fasting LDL cholesterol (mmol/L)

	Regression coefficient	95% confidence interval		p-value (two-tailed)
Age at assessment (years)	-0.04	-0.16	0.08	0.06
Gender (male versus female)	-0.13	-0.48	0.22	0.49
Body mass index	-0.04	-0.16	0.08	0.06
Non- excessive daily dietary refined carbohydrate intake	-0.14	-0.75	0.47	0.65
Non- excessive daily dietary fat intake	-0.47	-1.39	0.45	0.32
Recent efavirenz exposure §	0.91	0.20	1.62	0.01
Recent stavudine exposure §	-0.26	-0.71	0.19	0.26
Cumulative efavirenz exposure (for each additional year)	-0.04	-0.24	0.24	0.78
Cumulative lopinivir/r exposure (for each additional year)	0.24	0.00	0.48	0.03
Cumulative stavudine exposure (for each additional year)	0.12	-0.12	0.36	0.12
Cumulative exposure to any ART (for each additional year)	-0.12	-0.36	0.12	0.22

§ Defined as current exposure or exposure within the previous six months

Multivariate Regression model of the predictors of fasting LDL cholesterol (mmol/L)

Conclusions: Prevalences of insulin resistance and dyslipidemia were high. Cumulative lopinovir is an independent risk factor for dyslipidemia, with efavirenz exposure having only transitory effect. ART-induced dyslipidemia and insulin resistance occur independently of lipoatrophy and should not be coalesced under the label "Lipodystrophy Syndrome".

930 Growth and Lipid Profiles in a South African Cohort of HIV$^+$ Children and HIV$^-$ Controls

Sarah Ramteke[1]; Stephanie Shiau[1]; Marc Foca[1]; Renate Strehlau[2]; Francoise Pinillos[2]; Faeezah Patel[2]; Avy Violari[3]; Afaaf Liberty[3]; Stephen M. Arpadi[1]; Louise Kuhn[1]

[1]*Columbia University, New York, NY, US;* [2]*University of the Witwatersrand, Johannesburg, South Africa;* [3]*University of Witwatersrand, Johannesburg, South Africa*

Background: Prior studies from sub-Saharan Africa report elevated lipids and different patterns of regional fat distribution in perinatally HIV$^+$ children receiving ritonavir-boosted lopinavir (LPV/r) compared to non-nucleoside reverse transcriptase inhibitors (NNRTIs); however, interpretation of findings is limited by lack of comparison data from HIV$^-$ children. Here, we compare lipid profiles and body composition between HIV$^+$ children (stratified by LPV/r vs NNRTIs) and HIV$^-$ controls.

Methods: The Childhood HAART Alterations in Normal Growth, Genes, and aGing Evaluation Study (CHANGES) is a longitudinal cohort study of perinatally HIV$^+$ children and HIV$^-$ controls aged 4-9 years in Johannesburg, South Africa. At enrollment, anthropometrics, viral load, CD4, total cholesterol (TC), HDL, LDL, and triglycerides (TG) were measured. Weight- (WAZ), height- (HAZ), and BMI-for-age (BAZ) z-scores (per WHO) were calculated. US pediatric thresholds for dyslipidemia were used.

Results: 553 HIV$^+$ children (46% male, median age 6.9 years) and 300 controls (54% male, median age 7.0 years) were enrolled. Of the HIV$^+$ children, 94.8% were on antiretroviral therapy (ART) (69.6% on LPV/r and 30.2% on NNRTIs) and 85.9% had undetectable plasma HIV RNA; median CD4% was 34.4. Compared to controls, mean WAZ was lower in HIV$^+$ children (-0.7 vs -0.3, p<0.01), a greater proportion of HIV$^+$ children were stunted (HAZ <-2) (18.4 vs 9.3%, p<0.01), and a smaller proportion were overweight (BAZ>1) or obese (BAZ>2) (14.9 vs 21.7%, p=0.01). Whether on LPV/r or NNRTIs, a higher proportion of HIV$^+$ children had borderline/elevated TC or abnormal TG than controls, although a higher proportion of those on LPV/r had borderline/elevated TC, borderline/elevated LDL, or abnormal TG than those on NNRTIs. A greater percentage of children on LPV/r had borderline/elevated LDL than controls (**Table**).

Table: Lipid Profile at CHANGES Study Enrollment, by HIV Status and Regimen (LPV/r vs NNRTIs)

Measurement (mg/dL)	N (%)				*p*-value			
	HIV-infected			Controls (n=300)	LPV/r vs NNRTIs	HIV-infected vs Controls	LPV/r vs Controls	NNRTIs vs Controls
	All (n=553)	LPV/r (n=364)	NNRTIs (n=158)					
Total Cholesterol								
Acceptable: (<170)	269 (48.9)	148 (41.0)	94 (59.5)	229 (76.3)	<0.01	<0.01	<0.01	<0.01
Borderline/Elevated: (≥170)	281 (51.1)	213 (59.0)	64 (40.5)	71 (23.7)				
LDL								
Acceptable: (<110)	384 (69.8)	228 (63.2)	126 (79.8)	259 (86.6)	<0.01	<0.01	<0.01	0.06
Borderline/Elevated: (≥110)	166 (30.2)	133 (36.8)	32 (20.3)	40 (13.4)				
HDL								
Abnormal: (<35)	38 (6.9)	21 (5.8)	7 (4.4)	21 (7.0)	0.52	0.96	0.53	0.28
Normal: (≥35)	512 (93.1)	340 (94.2)	151 (95.6)	279 (93.0)				
Triglycerides								
Normal: (≤150)	424 (77.1)	266 (73.7)	132 (83.5)	275 (91.7)	0.01	<0.01	<0.01	0.01
Abnormal: (>150)	126 (22.9)	95 (26.3)	26 (16.5)	25 (8.3)				

**Note: Denominators are as shown*

Conclusions: In a South African cohort of HIV$^+$ children and population-appropriate HIV$^-$ controls, HIV$^+$ children were of smaller size than controls. Unfavorable alterations in lipid profiles were detected in HIV$^+$ children on LPV/r as well as those on NNRTIs compared to controls. In light of childhood origins of CVD and the need for HIV$^+$ children to remain on lifelong ART, strategies for early life management of lipid alterations may be warranted.

THURSDAY, FEBRUARY 26, 2015

Session P-U7 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Complications of HIV and ART: Bones, Brains, and Kidneys

931 Vitamin D Status and Bone Outcomes in Perinatally HIV-Infected Children

Denise L. Jacobson[1]; Mitchell Geffner[2]; Charles B. Stephensen[3]; Rohan Hazra[4]; Kunjal Patel[8]; Tracie L. Miller[5]; Russell B. Van Dyke[6]; Angela Ellis[9]; Linda A. DiMeglio[7]
For the Pediatric HIV/AIDS Cohort Study

[1]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [2]Children's Hospital Los Angeles, Keck School of Medicine, Los Angeles, CA, US; [3]USDA, Davis, CA, US; [4]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, US; [5]University of Miami, Miami, FL, US; [6]Tulane University School of Medicine, New Orleans, LA, US; [7]Indiana University, School of Medicine, Indianapolis, IN, US; [8]Harvard School of Public Health, Boston, MA, US; [9]Frontier Science and Research Foundation, Amherst, NY, US

Background: HIV-infected children (HIV+) are at risk for poor bone mineral accrual, but the predisposing etiological factors are ill-defined. We previously reported lower than recommended intakes of vitamin D in over half of HIV+ children enrolled in the US-based Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol (AMP) (DiMeglio 2013). In this study, we hypothesized that serum 25-hydroxy vitamin D (25D) levels would be lower in HIV+ children than HIV-exposed uninfected (HEU) children and would be associated with lower bone mineral density (BMD) in HIV+ children.

Methods: We measured serum levels of 25D, parathyroid hormone (PTH), calcium, and phosphate in perinatally HIV+ (N=426) and HEU (N=219) children. Dual-energy X ray absorptiometry (DXA) was performed in HIV+ to assess total body and spine BMD and percent body fat. Z-scores were calculated for bone measures based on reference data. Among HIV+ children, 396 had a DXA scan within 365 days of the 25D assay. Low serum 25D was defined as < 20 ng/mL. The prevalence ratio (PR) and 95% confidence interval (95%CI) of low 25D in HIV+ relative to HEU children was determined as were associations of 25D levels with BMD outcomes in HIV+ children, unadjusted and adjusted for confounding.

Results: The median age of the HIV+ and HEU children was 13.0 and 10.7 years, respectively. The majority of children were Non-Hispanic Black (62%) or Hispanic (28%). Prevalence of low 25D was 43% in HIV+ versus 34% in HEU children (P=0.027), with a prevalence ratio of 1.27 (95%CI 1.02, 1.58) and 1.14 (95%CI 0.93, 1.41) unadjusted and adjusted, respectively. On univariable analysis, low 25D was associated with older age, Non-Hispanic Black race/ethnicity, female sex, born on mainland US versus Puerto Rico, winter or spring season, and higher total body fat % by DXA. In children with low 25D, mean level of PTH was higher and calcium and phosphate levels were lower. Among HIV+ children, for each 1 ng/mL decrease in 25D level there was a 0.013 SD decrease in total body BMD z-score (P=0.079), adjusted for confounders (age, race/ethnicity and height). No association was observed between 25D and spine BMD z-score (adjusted estimate 0.0042, P=0.56).

Conclusions: Low 25D is common in both HIV+ and HEU children. There was a trend for an association between vitamin D deficiency and lower total body BMD in HIV+ children. HIV+ children should be monitored routinely for 25D deficiency due to possible adverse effects on BMD.

932 Bone Quality by Ultrasonometry in South African HIV+ Children and HIV- Controls

Stephen M. Arpadi[1]; Stephanie Shiau[1]; Renate Strehlau[2]; Francoise Pinillos[2]; Faeezah Patel[2]; Louise Kuhn[1]; Ashraf Coovadia[2]; Sarah Ramteke[1]; Jonathan Kaufman[3]; Michael T. Yin[1]

[1]Columbia University, New York, NY, US; [2]University of the Witwatersrand, Johannesburg, South Africa; [3]Mount Sinai School of Medicine, New York, NY, US

Background: Due to limited access to dual x-ray absorptiometry (DXA), few studies have described bone quality among HIV+ children in resource-limited settings (RLS), where the majority of HIV-infected children reside. Quantitative ultrasonography (QUS) is portable, relatively inexpensive, quick, simple to use and does not involve radiation exposure, making it well-suited for monitoring and evaluating bone acquisition in RLS. Although data are limited, QUS appears to have good agreement with DXA. We compare bone quality by QUS of South African HIV+ children receiving antiretroviral therapy (ART) to healthy HIV- children recruited as a control group.

Methods: Data were obtained from the bone sub-study (79% of target sample accrued) of CHANGES (Childhood HAART Alterations in Normal Growth, Genes, and aGing Evaluation Study), a longitudinal study of perinatally HIV+ children and HIV- controls in Johannesburg, South Africa. Weight- (WAZ), height- (HAZ), and BMI-for-age (BAZ) z-scores were calculated using WHO standards; CD4 and HIV-1 RNA levels were measured. Speed of sound (SOS) and broadband ultrasound attenuation (BUA) at the heel/calcaneus were measured by QUS (Lunar Achilles Insight). Calcaneus stiffness index (SI) was calculated as per manufacturer: SI = (0.67 x BUA + 0.28 x SOS) – 420.

Results: 206 HIV+ children (49.5% male) and 140 controls (55% male) were included in this analysis. HIV+ children were younger than controls (mean age 6.4±1.3 vs 7.2±1.5 years, p<0.01). All HIV+ children were on ART (52% PI-based, 48% NNRTI-based regimens; none receiving tenofovir; mean duration on ART 5.7±1.1 years), 72% had undetectable HIV-1 RNA levels, and median CD4% was 37.7. HIV+ children had lower mean WAZ (-0.8 vs -0.4, p<0.01) and HAZ (-1.4 vs -0.9, p<0.01) than controls. Median SOS was similar between HIV+ and HIV- children (1580 vs 1573, p=0.15). Unadjusted mean BUA was lower in HIV+ than HIV- children (71.5 vs 84.3, p<0.01) and remained lower after adjustment for age, sex, weight, and height (p<0.01). Unadjusted mean SI was also lower in HIV+ than HIV- children (78.5 vs 82.0, p=0.03), remaining lower after adjustment for age, sex, weight, and height (78.6 vs 81.9, p=0.048).

Conclusions: In this South African sample of school aged children, lower indices of bone quality by QUS are detectable among HIV+ children receiving ART compared to HIV- controls. QUS may prove to be a valuable method to assess bone quality and acquisition in HIV-infected children in RLS.

933 APOL1 Gene Variants and Chronic Kidney Disease in Perinatally HIV-Infected Youth

Murli Purswani[1]; Kunjal Patel[2]; Cheryl Winkler[3]; Stephen Spector[4]; Rohan Hazra[5]; George Seage[2]; Lynne Mofenson[5]; Gwendolyn Scott[6]; Russell Van Dyke[7]; Jeffrey Kopp[8]
For the Pediatric HIV/AIDS Cohort Study (PHACS)

[1]Albert Einstein College of Medicine, Bronx, NY, US; [2]Harvard School of Public Health, Boston, MA, US; [3]National Cancer Institute (NCI), Bethesda, MD, US; [4]University of California San Diego, San Diego, CA, US; [5]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, US; [6]University of Miami, Miami, FL, US; [7]Tulane University, New Orleans, LA, US; [8]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, US

Background: Two coding variants, G1 and G2, in the *APOL1* gene are present at high frequency in Sub-Saharan African populations. Studies in adults and children have repeatedly demonstrated strong associations between these alleles, operating in a recessive manner, and various glomerular diseases including HIV-associated nephropathy. We explored associations between *APOL1* variants and chronic kidney disease (CKD) in youth with perinatal HIV infection (P-HIV).

Methods: We carried out a nested case-control study within the PHACS Adolescent Master Protocol, a prospective study of children and youth with P-HIV. Using salivary DNA *APOL1* risk alleles (RAs) were genotyped. Race was collected by self-report. Continental ancestry was determined by genotyping 41 ancestry-informative markers and classified as Africa, Europe, America, South/Central, South/West, and East Asia, and Oceania. CKD was defined as ≥2 sequential urine protein/creatinine ratios ≥0.2 g/g (or dipstick protein ≥1+), or ≥2 sequential estimated GFRs <60 mL/min/1.73m^2 (Schwartz equation) not followed by a normal value, or a history of disease (nephropathy, nephrotic syndrome, chronic renal failure and focal segmental glomerulosclerosis). P-HIV controls had no evidence of kidney disease. Fisher's Exact test was used to compare RAs (2 versus 0/1 for G1 combined with G2) by case status using crude odds ratios (OR) and further adjusted for African ancestry (AAnc).

Results: Of 448 P-HIV participants, 234 met case/control criteria yielding 27 CKD cases and 207 controls. 70% self-identified as black, 23% white; 41% were male. Mean (area under the curve estimate) HIV viral load difference between cases and controls was 4.07 logs (95% confidence interval [CI]: –1.34 to 7.45). There was a trend for association between self-reported black race and CKD (OR: 3.0; 95% CI: 0.9-10.5). Among blacks carriage of 2 *APOL1* RAs was 13%; among whites, none had 2 RAs, but 11% had 1 RA. Further, proportion of AAnc (0.71-0.8) was associated with CKD (OR: 8.8; 95% CI: 1.9-41.4). Association between *APOL1* RAs (2 vs 0/1) with CKD was significant in those who self-reported as black (OR: 3.2; 95% CI: 1.2-9.0), and in the overall study population (OR: 4.1; 95% CI: 1.5-11.2). These findings remained significant when adjusted for proportion of AAnc (OR: 3.5, 95% CI: 1.2-10, overall population), suggesting that the *APOL1* association is specific for this gene rather than simply tracking AAnc.

Conclusions: Carriage of 2 *APOL1* risk alleles increases risk for CKD in youth with P-HIV.

934 Cystatin C Is a Marker for Both Inflammation and Renal Function in HIV+ Children

Àngela Deyà-Martínez[1]; **Clàudia Fortuny**[1]; Pere Soler-Palacín[2]; Olaf Neth[3]; Emilia Sánchez[4]; Andrea Martín-Nalda[2]; Lola Falcón-Neyra[3]; Anna Vila[1]; Anna Valls[1]; Antoni Noguera-Julian[1]

[1]Hospital Sant Joan de Déu, Esplugues, Spain; [2]Hospital Vall d'Hebrón, Barcelona, Spain; [3]Hospital Virgén del Rocío, Sevilla, Spain; [4]Universitat Ramon Llull, BArcelona, Spain

Background: Renal toxicity and other non-AIDS conditions are leading causes of morbidity and mortality in HIV-infected adults in the HAART era. Cystatin C has been proposed as a more sensitive marker of renal function in this population, but may be affected by ongoing inflammation. We aimed to study cystatin C levels and how they correlate with classic markers of renal function and inflammatory factors in a cohort of HIV-infected pediatric patients.

Methods: Multicentre cross-sectional observational study conducted in a cohort of HIV-infected children and adolescents followed-up in 3 pediatric centers in Spain. Renal function was assessed by means of first morning urine protein/creatinine and albumin/creatinine ratios and creatinine-estimated glomerular filtration rates (eGFR), together with the following inflammatory markers: reactive C protein, beta-2-microglobulin and 25(OH)-vitamin D levels. Plasma cystatin C was measured using a turbidimetric inmunoassay (Multigent cystatin C assay; Abbott Diagnostics, Wiesbaden, Germany; normal values <1.38 mg/L). A control group of sex- and age-matched healthy children and adolescents was used.

Results: Overall, 83 HIV-infected patients (51 females, mean age 12.7y) and 49 controls were included. At assessment, mean CD4 cell count was 921/mmcc, 29 patients had a previous AIDS diagnosis, 73 were on HAART (including tenofovir in 28) and HIV viremia was undetectable in 61. No patient presented symptoms consistent with urinary protein loss or renal damage. No differences in renal function and cystatin C levels were observed between patients and controls.

In univariate analysis among HIV-infected patients, higher cystatin C levels were associated with no previous AIDS diagnosis (0.89 vs 0.81 mg/L; p=0.05), previous indinavir exposure (1.11 vs 0.87 mg/L; p=0.02), detectable viral load (0.91 vs 0.87 mg/L; p=0.08) and naïve status (0.96 vs 0.87 mg/L; p=0.07). Significant correlations were also observed between cystatin C and eGFR (r=-0.27; p=0.01) and beta-2-microglobulin (r= 0.569; p< 0.01). In multivariate analysis, adjusted by undetectable viremia (yes/no), eGFR (p=0.014), beta-2-microglobulin levels (p=0.001) and prior use of indinavir (p=0.012) remained as independent risk factors for higher cystatin C values.

Conclusions: In our study, cystatin C values were associated with eGFR and beta-2-microglobulin. This suggests that cystatin C may be useful as a marker of renal function in HIV-infected pediatric patients, independently of ongoing inflammation or viremia.

935 Cognitive Performance and Intracerebral Findings in Perinatally HIV-Infected Children

Sophie Cohen[1]; Matthan W. Caan[2]; Jacqueline A. ter Stege[3]; Henriette J. Scherpbier[1]; Taco W. Kuijpers[1]; Peter Reiss[2]; Gert J. Geurtsen[2]; Charles B. Majoie[2]; Ben Schmand[2]; Dasja Pajkrt[1]

[1]Emma Children's Hospital AMC, Amsterdam, Netherlands; [2]Academic Medical Center University of Amsterdam, Amsterdam, Netherlands; [3]Emma Children's Hospital, Amsterdam, Netherlands

Background: Despite the declined incidence of severe neurological complications such as opportunistic infections and HIV-encephalopathy, HIV-infection in children is still associated with a range of cognitive problems. Studies comparing HIV-infected children to socioeconomically (SES) and ethnicity-matched controls are lacking, whereas these are important confounding factors in the context of cognitive functioning. In addition, advanced magnetic resonance imaging (MRI) may serve as a non-invasive tool to gain more insight in the cognitive deficits, and studies using MRI in HIV-infected children are scarce.

Methods: HIV-infected children were included from the outpatient clinic of the Emma Children's Hospital AMC, Amsterdam. Healthy, HIV-unaffected controls were matched to age, gender, ethnicity, and SES. All participants completed a comprehensive neuropsychological assessment (NPA) evaluating intelligence, information processing speed,

attention, memory, executive- and visual-motor functioning. Subsequently, all participants underwent an advanced 3TESLA MRI-scan for the evaluation of intracerebral volumes and white matter integrity. White matter integrity was measured by MRI sequences for white matter diffusivity and white matter hyperintensities.

Results: In total, 35 perinatally HIV-infected (median age: 13.8 years, median $CD4^+$ T-cells: $770*10^6$/L, 89% on cART, 83% with an undetectable HIV VL) and 37 healthy children (median age: 12.1 years) were included. HIV-infected children performed poorer on all cognitive domains (Table 1), and had a lower grey matter volume (HIV: 666.3 cm^3, SD 56.7; healthy: 699.9 cm^3, SD 74.5, p=0.023), a higher white matter diffusivity (HIV: $8.0x10^{-4}$, SD 0.3; healthy: $7.7x10^{-4}$, SD 0.2, p<0.001) and more white matter hyperintensities (HIV: 59%; healthy: 18%, p<0.001).

Cognitive domain	Neuropsychological test	HIV-infected (n=35)		Healthy (n=37)		d	*P*-value*
		Mean (SD)	Range	Mean (SD)	Range		
Intelligence	Verbal IQ	77.9 (15.7)	54-112	89.6 (13.6)	53-117	0.8	0.003
	Performance IQ	78.1 (15.5)	54-123	86.5 (16.2)	55-123	0.5	0.030
	Total IQ	76.0 (15.7)	51-118	87.5 (13.6)	63-120	0.8	0.002
Information processing	Processing speed index	86.6 (14.9)	60-136	96.5 (16.2)	65-143	0.6	0.017
Attention span	Digit span scaled score	7.6 (3.2)	1-13	10.0 (2.6)	5-16	0.8	0.002
Visual-motor function	Beery VMI standard score	78.0 (16.7)	44-117	86.6 (13.6)	44-119	0.6	0.048
Memory	RAVLT recall^	40.1 (11.2)	19-60	44.4 (7.5)	27-60	0.5	0.043
Executive function	TMT B speed (sec)^	125 (163)	32-366	102.0 (69.7)	39-372	0.4	0.023

Test values per cognitive domain in all study participants.
Abbreviations: SD=Standard Deviation. D=Cohen's d (effect size) (≤0.2=small, 0.2-0.8=medium, ≥0.8=large). IQ: Intelligence quotient. TMT: Trail Making Test. Beery VMI: Beery-Buktenica developmental test of visual-motor integration. RAVLT: Rey's auditory verbal learning test. ^: raw score. *: *P*-value adjusted for age at assessment, gender and parents' educational level (ISCED).

Conclusions: Children with HIV had a lower grey matter volume and a decreased white matter integrity as compared to healthy, matched controls. These observations occur in the context of poorer overall cognitive functioning in the HIV-infected group, which warrants further studies investigating the explanatory value of brain volumes and white matter integrity for cognitive performance in HIV-infected children. More insight in the observed cognitive deficits and intracerebral alterations is essential as these factors may influence future intellectual performance, job opportunities and community participation of HIV-infected children.

936 Executive Functions Among Perinatally HIV-Exposed and HIV-Infected Youth

Sharon L. Nichols[1]; Miriam Chernoff[2]; Kathleen M. Malee[3]; Patricia A. Sirois[4]; Paige L. Williams[2]; Betsy L. Kammerer[5]
the Memory Substudy Team of the Pediatric HIV/AIDS Cohort Study (PHACS)

[1]University of California, San Diego, La Jolla, CA, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]Northwestern University Feinberg School of Medicine, Chicago, IL, US; [4]Tulane University School of Medicine, New Orleans, LA, US; [5]Children's Hospital Boston, Boston, MA, US

Background: Executive functions (EF), including organization, inhibition, and planning, are critical for management of daily activities. Evidence suggests HIV may impact EF in adults. The effect of perinatally acquired HIV (PHIV) on EF in children and youth is less well understood despite the potential importance of EF in everyday life, including academics, risk behavior management, medication adherence, and health care. This study compared EF in youth with PHIV and perinatally HIV-exposed but uninfected youth (PHEU).

Methods: Four Delis-Kaplan Executive Function System (D-KEFS) subtests were administered to 173 PHIV and 85 PHEU youth, ages 9-19, enrolled in a substudy of the PHACS Adolescent Master Protocol. Youth with PHIV, with and without a history of CDC Class C conditions (PHIV-C, n=45, and PHIV-non-C, n=128), were compared to each other and to PHEU youth. Associations with measures of current and past disease severity (HIV RNA, CD4%) were evaluated. Analyses used linear regression models implemented via generalized estimating equations, adjusting for demographic and socioeconomic covariates.

Results: The majority of participants were Black (77%); 18% were Hispanic, and 54% female. Mean ages at entry were 12.9 years (PHEU), 14.5 years (PHIV-non-C), and 15.5 years (PHIV-C). 75% of PHIV-non-C and 64% of PHIV-C had current HIV RNA <400 copies. After adjustment for potential confounders, the PHIV-C group was significantly (p<0.05) slower and made more errors on Inhibition and were significantly slower on the Color Naming/Reading Combined conditions of the Color-Word Interference subtest (see Table). This group also had significantly lower unadjusted, but not adjusted, scores on some verbal and visual fluency conditions; there were no differences for verbal problem-solving. PHIV-non-C and PHEU did not differ on any measure. Prior encephalopathy was associated with slower Verbal Fluency, Color Naming and Inhibition trial performance. Associations of test results with HIV RNA, CD4%, and age at greatest disease severity were complex.

Table. Adjusted Mean Differences Between Groups for Selected Color-Word Interference Conditions

	PHIV-C vs. non-C		PHIV-C vs. PHEU		PHIV-non-C vs. PHEU	
D-KEFS Color-Word Interference Condition	Mean difference (95% CI)	P-value	Mean difference (95% CI)	P-value	Mean difference (95% CI)	P-value
Color Naming/Reading Combined	-1.7 (-2.8,-0.6)	0.003	-1.8 (-3.0,-0.6)	0.004	0.0 (-0.9,0.8)	0.92
Inhibition	-1.1 (-2.3,0.1)	0.08	-1.5 (-2.7,-0.3)	0.02	-0.4 (-1.3,0.4)	0.35
Total Errors-Inhibition	-1.1 (-2.4,0.3)	0.12	-1.6 (-3.0,-0.2)	0.02	-0.6 (-1.5,0.4)	0.25

D-KEFS= Delis-Kaplan Executive Function System; CI=confidence interval

Conclusions: Youth with PHIV and a history of greater disease severity showed poorer performance on select measures of EF; however, observed lower EF skills in this population may be related in part to underlying factors such as cognitive speed and efficiency. Relationships of EF development with degree and timing of disease progression in childhood require further study. Implications for long-term outcomes and interventions are important avenues for follow-up.

937 Sleep Disturbances in a Cohort of HIV-Infected Children and Adolescents on Antiretroviral Treatment: NeuroCoRISpeS

Cristina García-Navarro[1]; Santiago Jiménez de Ory[2]; Maria Luisa Navarro Gomez[2]; José Tomás Ramos Amador[6]; Maria Jose Mellado[3]; Luis Prieto[5]; Pablo Rojo Conejo[1]; Esmeralda Nuñez[4]; **María Isabel González-Tomé**[1]
On behalf of the CoRISpeS,ÄìMadrid Cohort
[1]Hospital Universitario 12 de Octubre, Madrid, Spain; [2]Hospital Universitario Gregorio Marañón, Madrid, Spain; [3]Hospital Universitario La Paz, Madrid, Spain; [4]Hospital Regional Universitario Carlos Haya, Malaga, Spain; [5]Hospital Universitario de Getafe, Getafe, Spain; [6]Hospital Universitario Clinico San Carlos, Madrid, Spain; [7]Madrid, Madrid, Spain

Background: Sleep disorders have been reported in adults with HIV infection with a prevalence of at least 30%. Sleep quality (SQ) is very important in children and their daily functioning, although in HIV pediatric population scarce data are avalaible. Our objective was to assess SQ in our cohort and to determine the impact of antiretroviral therapy (ART).

Methods: HIV infected children and adolescents due to vertical transmission between 4 and 23 years old. They belonged to a national cohort (CoRISpeS) and were followed according to a standard protocol in several hospitals in Spain. Clinical characteristics, ART and adherence were registered. SQ was assessed through Pittsburgh Sleep Quality Index (PSQI), a questionnaire validated in Spanish population which assesses SQ and disturbances over a month. It scores for 7 components and one global score, distinguishing between good and poor sleepers. For the analysis, we divided the sample into two groups according to the treatment they were receiving (NRTI+NNRTI vs NRTI+PI) in order to assess the influence of ART profile. Univariate and multivariate analysis (logistic regression) were performed.

Results: 59 patients were evaluated. Median age: 16y (4,23), age at start of ART: 0.62y (0,14), 66% females, 63% caucasian, AIDS CDC category: 33.9% (13.6% encephalopathy). Median CD4 at baseline: 35% (1,59), CD4/CD8 1.0 (0,3.28), nadir CD4: 15% (0.5,45). Viral load <50cop/ml: 84.7%. Median time on HAART: 11.32 years (0.51,17). The most frequent regimen was 2NRTI+1NNRTI (46%, Efavirenz 43.9%), followed by 2 NRTI+1PI (41%). Good adherence: 83%. No differences were found in clinical and immunovirological variables or time of exposure to ART between both groups. We found poor SQ in 24%, being the most frequent complaints: Sleep disturbances (76.3%), Sleep latency (59.3%), Subjective SQ (57.6%) and Daytime dysfunction (51.8%). There were relationship between the use of NNRTI and Sleep latency (p=.006) and Habitual sleep efficiency (p=.031). Specifically, patients who took EFV presented longer sleep latency (p=.026). Age was also related to poorer SQ (p=.005). When we adjusted the analysis for age, relationship between the use of NNRTI and poorer SQ remained: Sleep latency (p=.027) and Efficiency (p=.088).

Conclusions: In our cohort sleep complaints are common. Mainly NNRTI and EFV seem to have an impact on SQ compared to PI regimens. We consider these results important in pediatric population due to the influence in daily functioning, school and cognitive performance.

WEDNESDAY, FEBRUARY 25, 2015

Session P-U8 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Tuberculosis and Other Coinfections in Children With HIV

938 Tuberculosis Among Children on Antiretroviral Therapy in Swaziland, 2004-2012

Melissa A. Briggs[1]; Andrew Auld[1]; Harrison Kamiru[2]; Harriet Nuwagaba-Biribonwoha[2]; Velephi Okello[3]; George Bicego[1]; Andrew L. Baughman[1]; Simon Agolory[1]; Tedd V. Ellerbrock[1]; Peter Ehrenkranz[4]
[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]Mailman School of Public Health, New York, NY, US; [3]Swaziland Ministry of Health, Mbabane, Swaziland; [4]US Centers for Disease Control and Prevention (CDC), Mbabane, Swaziland

Background: Tuberculosis (TB) is the most common preventable cause of death in people living with HIV (PLHIV). Screening for TB and treating it are therefore key life-saving measures in HIV care settings, especially in Swaziland where over 75% of TB cases are amongst PLHIV. This study evaluated the implementation of TB screening in children initiating antiretroviral therapy (ART) in Swaziland and assessed predictors of TB disease amongst those who developed TB after ART initiation.

Methods: We performed a retrospective chart review on a nationally representative sample of children ≤14 years old, who initiated ART during 2004–2010. Twelve of 28 ART clinics were selected using probability-proportional-to-size sampling; at these 12 clinics, charts were selected by simple random sampling. Data were weighted and survey procedures used to account for study design. Multivariable Cox proportional hazards regression was used to determine adjusted hazard ratios (aHRs) for potential predictors of incident TB.

Results: Of 2,008 ART enrollees included in the sample, 984 (49%) were female, median age was 5.0 (interquartile range: 1.6–8.8), and 168 (8%) were receiving TB treatment at the time of referral to the ART clinic. Among the 1,840 children not already receiving TB treatment, 349 (19%) had documentation of screening for ≥1 of five recommended TB symptoms prior to ART initiation. The proportion of patients screened for ≥1 TB symptom increased from 0/37 (0%) in 2004 to 154/559 (30%) in 2010 (p=0.004). Of the 349 screened, 135 (47%) were positive for cough, and 62 (19%) subsequently received TB treatment. After ART initiation, an additional 143 (7%) of all 2,008 children were diagnosed with TB. Significant predictors of TB post-ART initiation included age ≥5yrs (aHR 1.7; 1.2–2.3; reference <2 years), World Health Organization Stage IV (aHR 2.8; 1.1–7.0; reference stage I/II), and TB treatment at ART initiation (aHR 1.7; 1.1–2.5).

Conclusions: TB is common among children initiating ART in Swaziland. Although TB screening is improving, over two-thirds of children starting ART in 2010 were not screened. Older age, more advanced HIV/AIDS, and TB treatment at ART start were predictive of incident TB, the latter possibly indicating sub-optimal TB cure or ongoing TB transmission within the child's household. Further program strengthening is needed to ensure that all pediatric patients initiating ART are screened for TB, and that best-practice measures are used to prevent relapse or recurrence of TB disease.

939 Mycobacterium TB Disease in HIV-Infected Children Receiving LPV/r or NVP-Based ART

Moherndran Archary[1]; Linda Barlow-Mosha[2]; Avy Violari[3]; Jane Lindsey[4]; Lynne Mofenson[4]; Patrick Jean-Philipe[4]; Bonnie Zimmer[4]; Paul E Palumbo[5]
[1]University of KwaZulu-Natal, Durban, South Africa; [2]MUJHU Care Ltd/MUJHU Research Collaboration, Kampala, Uganda; [3]Perinatal HIV Research Unit, Johannesburg, South Africa; [4]Frontier Science, Amherst, NY, US; [5]Geisel School of Medicine at Dartmouth, Lebanon, NH, US

Background: In high TB burden countries, HIV-infected children are at risk of developing Mycobacterium tuberculosis (MTB) disease due to impaired immunity. We describe the incidence, clinical spectrum, antiretroviral (ART) management, adverse events and virologic suppression rates of children on ART initiating anti-TB therapy in IMPAACT P1060

Methods: IMPAACT P1060 was conducted at 9 sites in Africa and 1 in India. HIV-infected children (2m - 3yr) with no TB were randomized to NVP or LPV/r-based ART. Children developing incident TB during the study were taken off study drug and placed on alternative ART as per national guidelines, but remained in study follow-up. Poisson regression was used to test for differences in TB incidence rates by baseline characteristics and over time and McNemar's test to assess virologic suppression rates before and after TB therapy.

Results: 56 of 451 participants were diagnosed with TB during a median study follow-up of 4.6 yrs (3.1 events/100 person-years (PYs), 95% CI: 2.4 – 4.1). 10 (18%) cases were culture-confirmed, the remainder were clinical diagnoses. 43 of 56 (77%) cases were pulmonary, 5 (9%) were non-pulmonary, and 8 (14%) were immune reconstitution inflammatory syndrome TB. In a multivariable Poisson regression, TB incidence was higher in children <1yr at entry (p=0.05) but did not differ significantly by baseline CD4% (< vs. ≥ 25%, p=0.49) or randomized ART arm (LPV/r vs. NVP, p=0.21). Most TB cases occurred within 6m of study entry (13.4 events/100PYs), with rates decreasing over the follow-up period (≤ 2.9 events/100 PYs, p<0.001). ART was modified in 45/56 (80%) children: most (48%) switched to RTV-boosted LPV/r and 7 (13%) to efavirenz. 48 of the 56 children starting TB therapy had HIV-1 RNA measurements 10-36 wks (value closest to 24 wks) after starting TB therapy; 63% had HIV-1 RNA < 400 cp/ml before TB therapy vs. 75% after (p=0.11). 6/56 HIV/TB co-infected children (11%) experienced grade ≥3 adverse events, including 3 with decreased ANC, 1 with abnormal SGPT, 1 with low hemoglobin, and 1 with convulsions.

Conclusions: TB disease remains a major challenge in HIV infected children living in high TB burden countries. Age <1 yr and the first 6m following initiation of ART are associated with higher risk of MTB disease. Superboosting of LPV/r was the most common ART change, regardless of initial ART regimen, and TB therapy did not affect viral suppression.

940 Safety of Rifabutin in HIV/TB-Coinfected Children on Protease Inhibitor-Based ART

Holly E. Rawizza[1]; Kristin M. Darin[2]; Kimberly K. Scarsi[3]; Biobele Brown[4]; Regina Oladokun[4]; Nkiru David[5]; Sulaimon Akanmu[6]; Oluremi Olaitan[7]; Prosper Okonkwo[7]; Phyllis Kanki[8]
On behalf of the APIN PEPFAR Team

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [2]Northwestern University, Feinberg School of Medicine, Chicago, IL, US; [3]University of Nebraska Medical Center, Omaha, NE, US; [4]University College Hospital, Ibadan, Nigeria; [5]National Institute of Medical Research, Lagos, Nigeria; [6]Lagos University Teaching Hospital, Lagos, Nigeria; [7]AIDS Prevention Initiative in Nigeria, Abuja, Nigeria; [8]Harvard School of Public Health, Boston, MA, US

Background: Tuberculosis (TB) is the leading cause of death among HIV-infected children, yet treatment options for those requiring protease inhibitor (PI)-based antiretroviral therapy (ART) are suboptimal. Rifabutin is the rifamycin of choice for adults on PI-based ART; but only one study to-date has evaluated its use among children on PI-based ART, and 2 of 6 children developed treatment-limiting neutropenia.

Methods: Since 2008, rifabutin has been available for HIV/TB co-infected children requiring PI-based ART in the Harvard/APIN PEPFAR program in Nigeria. We performed a retrospective analysis to evaluate laboratory (absolute neutrophil count (ANC), hemoglobin, platelet count, alanine aminotransferase (ALT), and creatinine) and clinical toxicities at baseline (prior to rifabutin) and during rifabutin therapy. Toxicities were graded using the DAIDS pediatric adverse event scales.

Results: Between 2008-2012, 42 children received rifabutin-based TB therapy with PI (lopinavir/ritonavir)-based ART: 45% were female with median (IQR) baseline age of 1.5 (0.8-4.6) years, CD4 of 437 (226-779) cells/mm^3 and CD4% of 14% (8-22%); 19% were at WHO clinical stage 4; and 48% were already on ART at rifabutin start. 86% completed the expected rifabutin course with resolution of TB symptoms. At baseline, 24% of children had grade 3 or 4 neutropenia (n=2), anemia (n=7), or both (n=1), which resolved or improved on rifabutin in all except 1 with stable grade 3 anemia. During rifabutin therapy, 12% developed grade 3 or 4 toxicity: grade 4 neutropenia (n=1) developed after 1 month on rifabutin, but resolved at month 4 despite ongoing therapy; grade 3 neutropenia (n=2) developed after 3 and 5 months on rifabutin and resolved following completion; grade 4 anemia (n=1) developed in 1 patient with underlying hemoglobinopathy and persisted after rifabutin completion; and grade 3 thrombocytopenia (n=1) developed after 3 months on rifabutin and persisted after treatment completion. Neither grade 3 or 4 abnormalities in ALT or creatinine nor significant clinical toxicities were reported.

Conclusions: With clinical and laboratory monitoring, our data suggest that rifabutin is a safe option for TB therapy among children on PI-based ART. Severe toxicities were more frequent prior to rather than during rifabutin therapy. Infrequent severe toxicities observed with rifabutin resolved following completion of therapy in most cases. Additional research is urgently needed to further evaluate rifabutin safety and efficacy among children.

941 Skin Complaints in African Children Randomized to Stop or Continue Cotrimoxazole

Andrew Prendergast[1]; Mutsa F. Bwakura Dangarembizi[2]; Peter Mugyenyi[3]; Joseph Lutaakome[4]; Adeodata Kekitiinwa[5]; Diana M. Gibb[6]; Sarah Walker[6]
On behalf of the ARROW Trial Team

[1]Queen Mary University of London, London, United Kingdom; [2]University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe; [3]JCRC, Kampala, Uganda; [4]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda; [5]Baylor-Uganda, Kampala, Uganda; [6]MRC Clinical Trials Unit at University College London, London, United Kingdom

Background: Recurrent skin complaints are common in HIV-infected children in sub-Saharan Africa. Skin infections tend to be more severe and atypical, respond less well to treatment and relapse more frequently in HIV-infected compared to uninfected children, making management challenging and affecting quality of life. Whether cotrimoxazole (CTX) has a role in preventing skin conditions in HIV-infected children is not well reported from settings where microbial resistance rates to CTX are high.

Methods: Of 1206 children in the ARROW trial in Uganda/Zimbabwe, 758 were randomized to stop (n=382) or continue (n=376) daily CTX (open-label) after median(IQR) 2.1(1.8,2.2) years on ART. Eligible children were aged >3 years, on ART >96 weeks, currently on CTX, using insecticide-treated bednets if living in malaria-endemic areas and had no previous PCP. During 6-weekly clinic visits, a nurse symptom screen was undertaken. Skin complaints were categorized blind to randomization as bacterial infection; fungal infection; viral infection; dermatitis; papular pruritic eruptions (PPE); or other (blisters, desquamation, ulcers and urticaria). Proportions of children ever reporting each skin complaint were compared across randomized groups using logistic regression.

Results: At randomization, median(IQR) age was 7(4,11) years and CD4 was 33%(26,39) (vs 13%(8,18) pre-ART); 25%/59%/14% children had WHO stage 2/3/4 disease. Fewer children continuing CTX ever reported bacterial skin infections over median 2 years follow-up (15% vs 33% stop, OR=0.36 [95%CI 0.25-0.51] P<0.001), with similar marginal trends for PPE (10% vs 14%, OR=0.64 [0.42,1.01] P=0.06) and other skin complaints (20% vs 23%, OR=0.61 [0.34,1.10] p=0.10). There was no evidence of difference in fungal (P=0.41) or viral (P=0.21) infections or dermatitis (P=0.98). Bacterial skin infections were also reported at significantly fewer clinic visits between 6-120 weeks post-randomization (1.2% vs 3.0%, P<0.001). Independent of CTX, bacterial skin infections were more common in younger children, those from rural Entebbe or Harare vs urban Kampala, and those with lower height-for-age or CD4<500 at CTX randomisation (all P<0.05).

Conclusions: In addition to the significant benefits previously reported for reduced hospitalization/death, prolonged CTX prophylaxis in children on long-term ART reduces bacterial skin complaints despite high rates of microbial resistance and good immune reconstitution on ART, highlighting an additional benefit for CTX in sub-Saharan Africa.

942 Disease Progression and Response to Treatment in Vertically HIV/HVC Co-infected Patients

Talía Sainz[1]; Carolina Fernández McPhee[2]; Santiago Jimenez de Ory[1]; Pablo Rojo[3]; Maria del Carmen Otero[4]; Milagros Garcia Lopez-Hortelano[5]; Olaf Neth[7]; Jose Beceiro[8]; Maribel González Tomé[3]; María Luisa Navarro[6]
On behalf of the Spanish Cohort of HIV-Infected Children and Adolescents (CoRISpe)

[1]Hospital Universitario Gregorio Marañón, Madrid, Spain; [2]Hospital Ramón y Cajal, SEIM-Gesida, Madrid, Spain; [3]Hospital 12 de Octubre, Madrid, Spain; [4]Hospital La Fe, Valencia, Spain; [5]Hospital La Paz, Madrid, Spain; [6]Hospital Gregorio Marañón, Madrid, Spain; [7]Hospital Virgen del Rocio, Sevilla, Spain; [8]Hospital de Alcalá, Alcalá de Henares, Spain

Background: Background: HVC co-infection is a predictor of adverse outcomes in HIV-infected patients. However, few data are available regarding the natural history of vertically HIV/HVC co-infected children. We analyzed the situation of a cohort of perinatally HIV/HVC co-infected patients and their response to HVC treatment.

Methods: Cross-sectional study within the Spanish National Cohort of Vertically HIV-infected children (CoRISpe). Perinatally HIV-HVC co-infected children, adolescents and young adults with longitudinal follow-up data were included. Epidemiological, clinical and treatment related variables were analyzed.

Results: The study included 50 HIV/HVC co-infected patients from 16 different hospitals, 34 (68%) of them already transferred to adult units at the moment of inclusion. Mean age was 20±4.5 years, 56% female, 14% of subjects with a prior AIDS diagnosis. All but three were on ART, but only 88% had HIV-RNA <50 cop/mL. Median CD4 T-cell count was 788 cel/mm[516-980], CD4/CD8 ratio 0.77[0.5-1.2] and CD4 nadir 218 cel/mm[119-389]. Regarding HVC diagnosis, 66% corresponded to genotype 1, 21% to genotype 4, 11% to genotype 3 and 2% to genotype 2. Transient elastometry data (Fibroscan) were available for 40 patients; of them, 22 (55%) showed liver fibrosis stage F1, 9 (25%) F2, 3 (7.5%) F3 and 5 (12.5%) F4. Progression to F3 occurred at a median age of 18 years[14-19]. Only 15 patients had received treatment for HVC infection, at a median age of 17.4 years[14.8-19.4]. Nine of them corresponded to genotype 1, 3 to genotype 3 and 3 to genotype 4. Treatment reached sustained viral response only in 5 patients (33.3%), three had genotipe1 and 2 genotype 3, one of them after being retreated. Of treated patients, 4 had been diagnosed of liver fibrosis stage F1-F2 and one F3. Most treatment combinations included peg-interferon plus ribavirine. Only in two cases treatment included telaprevir and only one of them was successful. Two cases received non-pegilated interferon, alone or in combination with ribavirine, and both failed to reach sustained viral response.

Conclusions: Our results suggest that HVC co-infection in vertically HIV-infected patients progress slowly during childhood, and most patients reach adult units without liver fibrosis. However, approximately 20% of children progress to liver fibrosis, most of them at the end of adolescence. Rates of sustained viral response were very low in this unique cohort, arousing the need of new therapeutic approaches for this population.

943 Human Papillomavirus and Cervical Cytology in Perinatally Infected Asian Adolescents

Annette H. Sohn[1]; Stephen J. Kerr[2]; Rawiwan Hansudewechakul[3]; Wasana Prasitsuebsai[2]; Kulkanya Chokephaibulkit[4]; Truong V. Nguyen[5]; Thoa P. Le[6]; Thida Singtoroj[1]; Nittaya Phanuphak[7]; HPV in Adolescents Study[1]

[1]TREAT Asia/amfAR – The Foundation for AIDS Research, Bangkok, Thailand; [2]HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [3]Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand; [4]Siriraj Hospital, Mahidol University, Bangkok, Thailand; [5]Hung Vuong Hospital, Ho Chi Minh City, Viet Nam; [6]Children's Hospital 1, Ho Chi Minh City, Viet Nam; [7]SEARCH, Thai Red Cross AIDS Research Centre, Bangkok, Thailand

Background: Persistent human papillomavirus (HPV) infection is the cause of multiple cancers, and associated with HIV infection. The risks may be higher in perinatally infected (paHIV) versus HIV-negative (HIV-neg) adolescents because of long-standing immune deficiency. We compared the prevalence of HPV infection and cervical cytology abnormalities in a case-control study in Asia.

Methods: Available baseline data from female participants enrolled up to July 2014 from 5 centers in Thailand and Vietnam were included in this analysis. paHIV and HIV-neg females were matched by age and lifetime number of sexual partners. HPV genotyping was performed on cervical, anal, and oral samples using the LINEAR ARRAY test (Roche). Liquid-based cervical cytology was interpreted using 2001 Bethesda criteria. Between-group comparisons of proportions were made using a chi-square or Fisher's exact test.

Results: A total of 90 paHIV and 70 HIV-neg sexually active females with a median age of 18 (IQR 18-20) years were enrolled. The median number of partners in the previous 6 months was 1.0 (IQR 1–1), and the median lifetime partners was 2 (IQR 1–3) in both groups; 2 females in each group reported a history of receptive anal intercourse. In paHIV, the median CD4 cell count was 567 (IQR 358-765) cells/mm^3 and 57 (63%) had HIV-RNA <40 copies/mL; 81 were currently on antiretroviral therapy. The prevalence of any high-risk HPV infection in paHIV and HIV-neg was 40% vs. 30% (p=0.19) in cervical, 42% vs. 23% (p=0.01) in anal, and 6% vs. 4% (p=0.73) in oral samples. The most common high-risk HPV type in cervical samples among paHIV was HPV 16 (14% vs. 7% in HIV-neg; p=0.15); 26 (29%) paHIV and 13 (19%) HIV-neg had partially or completely concordant high-risk HPV in cervical and anal compartments (p=0.17). The prevalence was 17% vs. 1.5% for low-grade squamous intraepithelial lesion (LSIL), and 1.1% vs. 1.5% for high-grade SIL (HSIL) in paHIV vs. HIV-neg females. Compared to HIV-neg females, paHIV had higher prevalence of abnormal cervical cytology from low-grade squamous intraepithelial lesion (LSIL) and above (p=0.004).

Conclusions: paHIV females had a higher prevalence of LSIL+ than HIV-neg females. Anal high-risk HPV infection was common despite infrequently reported anal intercourse, which may be explained by concordant cervical and anal HPV infection. paHIV should be prioritized for HPV vaccination, whenever available.

944 Sexually Transmitted Infections in Youth With Controlled and Uncontrolled HIV

Andres F. Camacho-Gonzalez[1]; Miriam C. Chernoff[2]; Paige L. Williams[2]; Ann Chahroudi[1]; James M. Oleske[3]; Rana Chakraborty[1]; Shirley Traite[2]; Murli U. Purswani[4]; Mark J. Abzug[5]
On behalf of the IMPAACT P1074 Study Team

[1]Emory University School of Medicine, Atlanta, GA, US; [2]Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA, US; [3]Rutgers New Jersey Medical School, Newark, NJ, US; [4]Albert Einstein College of Medicine, Division of Pediatric Infectious Diseases, Bronx Lebanon Hospital Center, Bronx, NY, US; [5]University of Colorado School of Medicine, Division of Pediatric Infectious Diseases, Aurora, CO, US; [6]International Maternal Pediatric Adolescent AIDS Clinical Trials, Durham, NC, US

Background: Half of new sexually transmitted infections (STIs) and 26% of new HIV infections each year in the US occur in youth 13-24 years of age. Co-STIs are a risk factor for HIV acquisition and transmission, but there is lack of data on STI acquisition in adolescents and young adults (AYAs) with controlled or uncontrolled HIV infection.

Methods: We determined the incidence of STIs in HIV-infected AYAs 12.5-<25 years of age who participated in the IMPAACT P1074 prospective observational cohort study from April 2009-April 2014 and compared rates among individuals with controlled and uncontrolled HIV infection. Virologic and immunologic control was defined as a mean HIV-1 RNA viral load (VL) level of <500 copies/mL and mean CD4+ T-cell count >500 cells/μl over the year preceding STI diagnosis. Socio-demographic and HIV disease characteristics were summarized by descriptive statistics. Univariate and multivariable logistic regression models were applied to evaluate the association of virological and immunological control on occurrence of STIs and identify other associated risk factors.

Results: 1,061 participants met criteria for study participation (49% male, 61% black, and 87% perinatally HIV-infected, with a mean age of 18.4 years at first chart review (SD: 3.9 years)). Ninety-five participants had a history of STI prior to study entry; of the remaining 966, 93 had incident STIs for an incidence rate of 2.59/100 person-years. Human papilloma virus (HPV) and chlamydial infections were the most common STIs. Univariate analysis showed significantly higher risk for an incident STI in AYAs who were older (odds ratio (OR)=1.17), female (OR=2.04), horizontally HIV-infected (OR=3.88), and had a prior STI history (OR=3.48). Significantly higher STI risk was observed with lower mean CD4+ T-cell counts (OR=2.60 for ≤500 cells/μl) and higher mean VL (OR=1.88 for ≥500 copies/mL). In the multivariable model, having an incident STI continued to be associated with older age (adjusted OR (aOR)=1.09, p=0.01), female sex (aOR=2.78, p<0.001), horizontally-acquired HIV-infection (aOR=2.08, p=0.02), and mean CD4+ T-cell count ≤500 cells/μl (aOR=2.26, p=0.001), but not with higher VL.

Conclusions: Significant rates of new STIs among HIV-infected AYAs demonstrate the need for enhanced preventive interventions, including safe-sex practices and HPV vaccination. STI acquisition is associated with older age, female sex, horizontally acquired HIV infection, and lower CD4+ T-cell count.

TUESDAY, FEBRUARY 24, 2015

Session P-U9 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Responses to Vaccines in Children

945 Sustained Responses to Measles Revaccination in HIV-Infected Children on ART in Kenya

Laura Newman[1]; Anne Njoroge[1]; Bhavna Chohan[1]; Amalia Magaret[1]; Jonathan Gorstein[1]; Julie M. Overbaugh[2]; Dalton Wamalwa[3]; Elizabeth M. Obimbo[3]; Ruth W. Nduati[3]; Carey Farquhar[1]

[1]University of Washington, Seattle, WA, US; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [3]University of Nairobi, Nairobi, Kenya

Background: Despite recent advances in reducing measles incidence in Africa, a number of measles outbreaks have occurred in countries with high HIV prevalence. One hypothesis is that there is a growing population of measles-susceptible HIV-infected children. This study was conducted to determine the effectiveness of measles revaccination in HIV-infected children on ART.

Methods: In this prospective cohort study, HIV-infected children 15 months to 12 years of age on ART in Nairobi, Kenya received an additional measles vaccine. Questionnaires, physical examinations, and blood draws were completed at enrollment, one, 12, and 24 months after measles revaccination. Measles antibody concentrations were determined by enzyme-linked immunosorbent assay (ELISA) at all time points.

Results: Of 232 enrolled children, 228 (98%) had received at least 1 measles vaccine before 1 year of age. There were 123 (53%) males, median age was 7.5 years (interquartile range (IQR): 5.5–9.5), and median CD4% was 32 [IQR: 27–38]. All children were on ART, and median time on ART was 3.4 years (IQR: 1.8–4.9). At enrollment, 52 (23%) of 231 children had an HIV viral load ≥1,000 copies/mL. Before revaccination, 125 (54%) of 232 study participants had protective levels of measles antibody. Seropositivity was observed in 216/220 (98%) participants at one month post revaccination and 158/224 (70%) at 12 months post revaccination. Of the 187 participants with with currently completed laboratory results from 24 months post revaccination, 105 (58%) were seropositive. Seroconversion and sustained seropositivity among those seronegative at enrollment was 37% at 12 months post revaccination. In this group, children with an HIV viral load <50 copies/mL at enrollment were twice as likely to seroconvert at 12 months compared to those with an HIV viral load ≥1000 copies/mL (RR=2.04, 95% CI 1.01 – 4.10, p=0.047). A larger height-for-age z-score at enrollment was associated with seroconversion at 12 months (RR=1.24, 95% CI 1.04 – 1.48, p=0.016). Time on ART, age, gender, CD4%, and vitamin A status at enrollment were not significantly associated with seroconversion at 12 months.

Conclusions: Measles revaccination conferred short-term sustained antibody response in HIV-infected children receiving ART, especially those who had suppressed levels of HIV virus and those with increased height-for-age z-score. Periodic measles revaccination of HIV-infected children on ART may be necessary to confer long-term immunologic memory.

946 T-Cell Anergy and Activation Are Associated With Suboptimal Humoral Responses to Measles Revaccination in HIV-Infected Children on Antiretroviral Therapy in Nairobi, Kenya

Matthew B. Buechler[1]; Laura Newman[2]; Bhavna Chohan[3]; Anne Njorge[5]; Dalton Wamalwa[6]; Carey Farquhar[3]

[1]University of Washington, Seattle, WA, US; [2]University of Washington, Seattle, WA, US; [3]University of Washington, Seattle, WA, US; [4]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [5]Kenyatta National Hospital, Nairobi, Kenya; [6]University of Nairobi, Nairobi, Kenya

Background: HIV-infected children are less capable of mounting and maintaining protective humoral responses to vaccination against measles compared to HIV-uninfected children. This poses a public health challenge in countries with high HIV burdens. Administration of antiretroviral therapy (ART) and revaccinating children against measles is one approach to increase measles immunity in HIV-infected children, yet it is not effective in all cases. Immune system anergy and activation during HIV infection are factors that could influence responses to measles revaccination.

Methods: This work was nested within a larger study in which HIV-infected children on ART were revaccinated for measles when their $CD4^+$ T cell frequency reached 15% of total T cells. During clinic visits at the time of revaccination, one month post-revaccination and one year post-revaccination, serum was collected to assess levels of measles-specific IgG by ELISA and PBMC were collected.

We examined PBMC from 20 participants who were measles seronegative (measles-specific IgG antibody titer <350 mIU/mL) at enrollment and developed detectable measles antibodies one month after revaccination. Of the twenty participants, ten children maintained measles antibodies one year after revaccination (responders) and ten children did not exhibit detectable measles antibodies one year after revaccination (non-responders).

We utilized a flow cytometry-based approach to examine whether T cell anergy and activation were associated with the maintenance of measles-specific IgG antibodies generated in response to measles revaccination in cohort of HIV-infected children on ART in Nairobi, Kenya. T cells were identified as $CD3^+CD4^+$ ($CD4^+$ T cells) or $CD3^+CD4^-$ ($CD8^+$ T cells). T cells were identified as anergic by expression of PD1 and activated by coexpression of CD38 and HLADR.

Results: Children who sustained measles-specific IgG for at least one year after revaccination displayed significantly lower PD1 surface expression on $CD8^+$ T cells on a per-cell basis and exhibited less activated $CD4^+$ T cells compared to those unable to maintain detectable measles-specific antibodies. Children in both groups were similar in age and sex, $CD4^+$ T cell frequency, duration of ART treatment and HIV viral load at enrollment.

Conclusions: These data suggest that aberrant T cell anergy and activation are associated with the impaired ability to sustain an antibody response to measles revaccination in HIV-infected children on ART.

947 Molecular Profiles of CXCR5+ CD4 Memory T Cells Associated With Flu Vaccine Response

Lesley R. de Armas[1]; Nicola Cotugno[1]; Suresh Pallikkuth[1]; Alberto Cagigi[3]; Paolo Palma[2]; Paolo Rossi[2]; Savita Pahwa[1]

[1]University of Miami Miller School of Medicine, Miami, FL, US; [2]Children's Hospital Bambino Gesu, Rome, Italy; [3]Children Hospital Bambino Gesu, Rome, Italy

Background: HIV-infected patients of all ages consistently underperform in flu vaccine efficacy. Peripheral T follicular helper (pTfh) cells, a subset of CD4 T cells which provide help to B cells for developing into Ab secreting cells, are characterized by (CXC) motif chemokine R5 (CXCR5) expression. We previously demonstrated functional impairment of this subset in adult HIV+ flu vaccine non-responders (NR) (Pallikkuth Blood 2012). Microarray data from a pediatric HIV-infected cohort receiving the 2009/10 pandemic influenza vaccine revealed upregulation of CXCR5 in whole blood of vaccine responders (R) compared to NR 4 weeks post-vaccination. We hypothesized that pTfh play a role in Ab responses to the flu vaccine and investigated whether defects in pTfh function could be identified prior to vaccination.

Methods: Fluidigm BioMark RT-PCR was performed on pTfh cells from a cohort of virally suppressed, vertically infected HIV+ children who received the 2012 seasonal flu vaccine. PBMC from baseline (T0) were stimulated with H1N1 antigen (16h) and then sort-purified as 500 cell pools into PCR buffer. This technology allowed us to study a panel of 96 genes related to Tfh function, immune activation, TCR signaling, and co-stimulation/inhibition simultaneously in pTfh from R (n=7) and NR (n=9), compared to healthy controls (HC,

n=9). The patients in this cohort have been immunized annually and had sero-protective antibody titers at T0; R were defined as having hemagluttination inhibition titers >1:40, and >4-fold increase above T0 4 wks post-vaccination.

Results: There were no observed differences in frequencies of pTfh between the groups before or after in vitro stimulation (*p=0.9,* ANOVA). However, **t**ranscriptomic analysis of pTfh from HC and R demonstrated a response to H1N1 stimulation which was marked by increased or stable expression of Tfh-related genes (*MAF, IL21, BCL6*, *ICOS*) and TCR signaling genes (*CD3D*, *MAPK3*, *FYN*, *PKC A*), while in NR they were significantly downregulated after stimulation. Interestingly, pTfh from NR displayed higher levels of the inhibitory receptor *CTLA4* (*p=0.01*, student's t test) compared to R suggesting a possible mechanism for reduced responses to vaccination.

Conclusions: Targeted molecular profiling of pTfh in previously vaccinated HIV-infected children, *before* influenza vaccination revealed antigen-driven favorable gene expression selectively in R. These results suggest that quality rather than quantity of pTfh in the periphery is controlling responses to vaccination.

948 The Potential of BCG and HIV-TB Vaccines to Exacerbate HIV-1 Pathogenesis in Infants

Kara Jensen[1]; Koen K. Van Rompay[2]; William R. Jacobs[3]; Glenn Fennelly[3]; Katie Mollan[1]; Michael G. Hudgens[1]; Mike Piatak[4]; Michelle H. Larsen[3]; Kristina De Paris[1]

[1]University of North Carolina, Chapel Hill, NC, US; [2]California National Primate Research Center, University of California, Davis, CA, US; [3]Albert Einstein College of Medicine, New York, NY, US; [4]Frederick National Laboratory, Frederick, MD, US

Background: The only licensed vaccine to prevent tuberculosis infection, *Bacille Calmette Guérin (BCG),* can cause *Mycobacterium bovis* dissemination in HIV-1 infected infants. We previously demonstrated that a double-auxotroph *M. tuberculosis* strain (A*Mtb*), expressing SIV genes to potentially protect against both TB and SIV/HIV infections, is immunogenic and safe in SIV-infected neonatal macaques. Here, we tested vaccine efficacy against repeated low-dose oral SIV challenge to mimic breast milk HIV-1 transmission in human infants.

Methods: Infant rhesus macaques were orally immunized at birth with A*Mtb*-SIV and boosted ID with A*Mtb*-SIV at week 3 (n=6), IM with MVA-SIV at weeks 3 and 6 (n=8) or not boosted (n=5). BCG (n=7) or mock (n=11) groups were also included. Weekly low-dose oral SIV challenges were started at week 9. Plasma viremia was measured by RT-PCR and immune activation by flow cytometry and ELISA. The number of challenges until SIV infection were compared with an exact log-rank test, and viremia and immune activation outcomes with Kruskal-Wallis or Mann Whitney tests.

Results: A*Mtb*-SIV, A*Mtb*, and BCG versus mock vaccinated infants appeared to require fewer SIV exposures for infection. Although the risk of SIV infection per exposure was not statistically different, BCG recipients had higher peak viremia compared to A*Mtb* or A*Mtb*-SIV (p=0.001), or mock infants (p=0.009). Further, BCG and combined A*Mtb* vaccinated infants had significantly higher acute phase viremia AUC compared to mock animals (p=0.037 and 0.029, respectively). The frequency of potential SIV target cells, $CCR5^+CD4^+$T cells, was significantly higher in all vaccinated compared to mock infants at the time of SIV exposure. Mycobacteria vaccine-induced $CD4^+$T cell activation was supported also by elevated levels of CD69 (p<0.0001), HLA-DR (p=0.025), and Ki-67 (p=0.007) in vaccinated versus mock animals. Furthermore, plasma levels of IFN-g (p=0.028), sCD14 (p=0.0015) and sCD163 (p=0.0016) were increased in vaccinated compared to mock infants.

Conclusions: A single dose of live attenuated A*Mtb* or BCG at birth induced persistent immune activation in infant macaques that was unresolved nine weeks later. Novel TB vaccine candidates under development include highly replication-attenuated auxotroph strains of BCG that are similar to our A*Mtb* vaccines. To avoid potentially enhanced morbidity in HIV-1 infected infants, TB vaccine candidates should be thoroughly evaluated for their risk of inducing persistent immune activation.

TUESDAY, FEBRUARY 24, 2015

Session P-U10 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Pharmacokinetics, Safety, and Efficacy of ART in Children and Youth

949 Prediction of ARV Drug Clearance in Children

Frantz Foissac; Naïm Bouazza; Elodie Valade; Mailys De Sousa; Floris Fauchet; Sihem Benaboud; Deborah Hirt; Stéphane Blanche; Saïk Urien; Jean-Marc Treluyer

EA 08 Université Paris Descartes, Sorbonne Paris Cité, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, Paris, France, Paris, France

Background: Ethical difficulties to conduct clinical trials in pediatric populations lead to insufficient pharmacokinetics data especially in HIV-1 infected children. Several antiretroviral (ARV) drugs are thus still not recommended in young children which may result in use of "off-label" prescriptions. However, the pharmacokinetic profile differs widely from birth to adolescence as compared to adult and to predict accurate clearance values in children, especially in neonates and infants, could improve the rational in dosing decisions.

Methods: A systematic review of pharmacokinetic reports in pediatric populations was performed to gather drugs clearances from birth to adulthood. A single equation to describe the clearances maturation process was then developed. The analysis was performed using the nonlinear mixed-effect modeling program NONMEM. The model accuracy was evaluated on ARV drugs for which pediatric pharmacokinetic studies were previously published (i.e., *abacavir, atazanavir, emtricitabine, efavirenz, enfuvirtide, lamivudine, lopinavir, nelfinavir, nevirapine, stavudine, tenofovir* and *zidovudine).* Prediction errors were also compared to those obtained from weight-based allometric scaling.

Results: The maturation of clearances was best described by a model based on both weight and age and taking into account drug adult clearance value. Age-related maturation of clearance reached 90% of adult value within 1.5 years of life. For children aged more than 2 years both allometry and age/weight based model provided accurate predictions (prediction error < 15%). However, contrary to allometry, the prediction error of the age/weight based model stay accurate from 6 months to 2 years old. Indeed, for children aged less than 2 years, allometric scaling alone systematically overestimated clearances. Accounting for age improved the clearance prediction. A high uncertainty remained regarding the predicted ARV drugs clearance in children aged less than 6 months: 352% and 83% respectively for allometry and the age/weight based model.

Conclusions: This analysis established a single equation using adult clearance value as well as age and weight to predict ARV drug clearance in children older than 6 months.To accurately predict drug clearance in children aged less than 6 months where the enzyme maturation process are not fully mature, a more complex physiologically based model including the maturation of active-transporters and specific enzymes involved in absorption and/or metabolism should be investigated.

950 Use of Maraviroc in HIV-1-Infected Paediatric Patients in Clinical Practice

Claudia Palladino[1]; Maria Luisa Navarro Gomez[6]; Pere Soler-Palacín[5]; Maria Isabel Gonzalez-Tome[7]; Santiago Jimenez de Ory[6]; Maria Espiau[5]; Juan Antonio León-Leal[4]; Clàudia Fortuny[3]; Verónica Briz[2]
CoRISpe working group

[1]University of Lisbon, Lisbon, Portugal; [2]National Center for Microbiology, Madrid, Spain; [3]Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain; [4]Hospital Infantil Universitario Virgen del Rocío, Seville, Spain; [5]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [6]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [7]Hospital Universitario Doce de Octubre, Madrid, Spain

Background: Maraviroc (MVC) is the first CCR5-antagonist approved in 2007 in HIV-infected adult patients with CCR5-tropism, while it is still under evaluation in paediatric patients. Our aim was to evaluate the effectiveness, safety and tolerability of MVC-based salvage therapy outside clinical trials in HIV-1-vertically infected paediatric patients.

Methods: A multicenter retrospective study of 20 treatment-experienced children (n=6) and adolescents (n=14) followed at least for 20 weeks was performed. Immunological, virological and clinical status of patients at baseline and during follow-up was analyzed every 3-6 months. Individuals were monitored from baseline (i.e., the date of MVC initiation) until the administrative censoring date or MVC discontinuation if occurred.

Results: At baseline, median viral load (VL) and CD4+T-cell (CD4 count) were 3.8 log and 672 (25%) cells/μl (IQR:231–836) and 4.1 log and 315 (22%) cells/μl (IQR:175–657) in children and adolescents, respectively without significant differences. Patients mainly harboured an HIV-1 subtype B virus (85%) with confirmed CCR5 tropism. All patients but one presented extensive resistance profile with 10 (53%) patients showing triple drug class resistance mutations (NRTI/NNRTI/PI). At least 1 fully active drug was prescribed to 18 (95%) patients as backbone regimen, of whom 17 (85%) received MVC with one or more new drugs (DRV/r; ETR; RLT). Median follow-up with MVC was 116 weeks (IQR:25–198). Sixteen out of twenty (80%) patients reached undetectable VL [(median at 13 weeks, (5–35)] with a median decrease in VL from baseline of 1.7 log. Twelve out of sixteen (75%) maintained virological suppression for a median of 105 weeks (IQR:44–208) of which 9/12 (45%) patients maintained uVL until the end of the follow-up for a median of 132 (50-230) weeks. Immunological recovery was observed in 14/20 patients with median increase of 275 cells/μl (IQR:135–500). No adverse events related to MVC-based therapy were reported. MVC interruption was observed in 8 patients, because of virologic failure (n=4); simplification (n=3); poor adherence (n=1). Two patients experienced emergence of CXCR4 variants and one of dual/mixed variants. Laboratory abnormalities included ALT/AST elevation (n=7), hypercholesterolemia (n=9), hypertriglyceridemia (n=12).

Conclusions: MVC is useful as a salvage therapy in children and adolescents with extensive resitance profile leading to maintained virological suppression in up to 60% of our cohort patients.

951 Safety and Pharmacokinetics of Elvitegravir in HIV-1 Infected Pediatric Subjects

Joseph M. Custodio[1]; Victor Musiime[2]; Aditya Gaur[3]; Elizabeth McFarland[4]; Wasana Prasitsuebsai[5]; Lize Hellstrom[6]; Xuelian Wei[1]; Rebecca Begley[1]; Srinivasan Ramanathan[1]; Sean R. Bennett[1]

[1]Gilead Sciences, Inc., Foster City, CA, US; [2]Joint Clinical Research Centre, Kampala, Uganda; [3]St. Jude Children's Research Hospital, Memphis, TN, US; [4]University of Colorado Denver, Aurora, CO, US; [5]HIV - NAT, Bangkok, Thailand; [6]Be Part Yoluntu Centre, Cape Town, South Africa

Background: Safe and effective pediatric antiretroviral therapies are needed. Elvitegravir (EVG), a once-daily integrase inhibitor, is indicated in treatment-experienced HIV-1 infected adults when administered with a ritonavir (r)-boosted protease inhibitor (PI/r). The safety and pharmacokinetics (PK) of EVG were evaluated in a completed lead-in phase of a study in 6 to <11 year old HIV-infected subjects upon addition to a PI/r-containing background regimen consisting of at least 2 fully-active agents.

Methods: Treatment-experienced subjects 6 to <11 years of age, weighing ≥17 kg with suppressed viremia (HIV-1 <50 c/mL) or failing a current antiretroviral regimen (HIV-1 RNA >1,000 c/mL) received EVG (adult or pediatric formulation) once daily in addition to their background regimen including either lopinavir/r or atazanavir/r. The adult EVG dose (85 mg) was administered in subjects ≥30 kg and reduced to 50 mg in subjects ≥17 kg to <30 kg. Intensive PK was performed on or after Day 10 (steady state). EVG exposure (primarily AUC_{tau}) was compared to exposures in adults from EVG+PI/r Phase 3 trials by an analysis of variance using a mixed-effects model for parallel group design. Adverse events (AE) and routine laboratory tests were assessed.

Results: A total of 14 subjects (57% male, 14% Asian, 71% black and 14% white) were enrolled with a median age of 10 years (range: 6-11) and a median weight of 26 kg (range: 18-47). At baseline, mean CD4 count was 811 cells/μL; 13 of 14 subjects had HIV RNA <50 c/mL. There were no deaths or AEs leading to premature study drug discontinuation. No EVG-related SAEs were observed. No AE occurred in more than one subject. EVG PK is summarized in Table 1. The geometric mean ratio (GMR) of EVG AUC_{tau}, C_{max}, and C_{trough} was 136%, 147%, and 129%, respectively, versus adult exposure. Importantly, mean EVG C_{tau} was ~11-fold above the in vitro protein-binding adjusted IC_{95} (44.5 ng/mL). Moreover, subjects ≥30 kg or ≥17 kg to <30 kg (receiving EVG 85 or 50 mg, respectively) showed EVG exposure associated with safety and efficacy based on extensive PK-pharmacodynamic analyses in adults. These study data are consistent with EVG PK in children ≥12 years of age.

Table 1. Pharmacokinetic Parameters and Statistical Comparison of EVG in HIV-1 Infected Pediatric Subjects versus Adult Subjects

EVG PK Parameter	EVG + PI/r Pediatric Subjects (Test) Mean (%CV)	EVG + PI/r Adult Subjects (Reference; n=334) Mean (%CV)	GMR (%)	90% CI (%)
All Subjects (n=14)				
AUC_{tau} (ng•h/mL)	24100 (30)	18000 (37)	136	(117, 159)
C_{max} (ng/mL)	2020 (30)	1380 (28)	147	(127, 169)
C_{trough} (ng/mL)	494 (53)	378 (57)	129	(96.1, 174)
Subjects ≥ 30 kg (n=6)				
AUC_{tau} (ng•h/mL)	27400 (21)	18000 (37)	159	(131, 192)
C_{max} (ng/mL)	2200 (27)	1380 (28)	160	(125, 205)
C_{trough} (ng/mL)	614 (41)	378 (57)	175	(123, 248)
Subjects ≥ 17 kg to < 30 kg (n=8)				
AUC_{tau} (ng•h/mL)	21600 (36)	18000 (37)	121	(96.2, 153)
C_{max} (ng/mL)	1890 (32)	1380 (28)	137	(113, 167)
C_{trough} (ng/mL)	405 (61)	378 (57)	103	(65.7, 162)

Conclusions: Administration of EVG once daily with a PI/r in children 6 to <11 years old provides therapeutic EVG exposure with mean trough concentrations ~11-fold above IC_{95} and appears well tolerated. These results support continued evaluation of the efficacy and safety of EVG in pediatric populations.

952 Lack of Emergent Resistance in HIV-1-Infected Adolescents on Elvitegravir-Based STRs

Danielle P. Porter; Sean R. Bennett; Erin Quirk; Michael D. Miller; Kirsten L. White

Gilead Sciences, Inc., Foster City, CA, US

Background: GS-US-236-0112 and GS-US-292-0106 are international, ongoing, phase 2/3, open-label, single arm, 48-week studies evaluating the safety and efficacy of the integrase inhibitor-based single-tablet regimens (STRs) elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF) and elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) in HIV-1 infected treatment-naïve adolescents. Here, we present resistance results from a planned Week 24 interim analysis.

Methods: Genotypic analyses of HIV-1 protease (PR), reverse transcriptase (RT) and integrase (IN; GS-US-292-0106 only) were performed at screening for both studies. Subjects with resistance to study drugs were excluded. Subjects in the postbaseline resistance analysis population (subjects with HIV-1 RNA ≥400 copies/mL at virologic failure) had genotypic/phenotypic analyses at failure for PR, RT, and IN.

Results: The Week 24 interim analysis included 21 subjects on E/C/F/TDF and 23 subjects on E/C/F/TAF. Most subjects on E/C/F/TDF had HIV1 subtype C (47.6%, 10/21) or B (38.1%, 8/21) with subtype AE also present (14.3%, 3/21). Most subjects on E/C/F/TAF had HIV1 subtype A1 (56.5%, 13/23) with the remainder having subtype AE (17.4%, 4/23), B (17.4%, 4/23), D (4.3%, 1/23), or complex mixtures (4.3%, 1/23). HIV-1 subtype distribution correlated with geography (A1, Uganda; AE, Thailand; B, USA; C, South Africa). Resistance mutations detected at baseline (not excluded at screening) are shown in Table 1. At Week 24, 85.7% (18/21) of subjects on E/C/F/TDF and 91.3% (21/23) on E/C/F/TAF had virologic success (HIV-1 RNA <50 c/mL) by FDA snapshot. Virologic response rates were similar across subtypes. Enrolled subjects with pre-existing IN-, NNRTI-, NRTI-, and PI-associated resistance mutations had virologic response rates similar to the overall study population (Table 1). One subject on E/C/F/TDF (4.8%, 1/21) and no subjects on E/C/F/TAF (0/23) met the criteria for postbaseline resistance analysis; no emergent resistance was detected. No subjects in either study experienced suboptimal virologic response.

Table 1. Resistance mutations detected at baseline and virologic success rates at Week 24.

Resistance Mutations at Baseline	GS-US-236-0112 E/C/F/TDF n=21		GS-US-292-0106 E/C/F/TAF n=23	
	Total Number of Subjects with Mutations	Subjects with Virologic Success at Week 24	Total Number of Subjects with Mutations	Subjects with Virologic Success at Week 24
Primary PI-Associated	0	n/a	0	n/a
Secondary PI-Associated	20	17/20[a]	23	21/23[b]
NNRTI-Associated	3	2/3[b]	2	2/2
NRTI-Associated	0	n/a	4	4/4
Primary INSTI-Associated	ND	n/a	0	n/a
Secondary INSTI-Associated	ND	n/a	5	4/5[b]

ND: no data, n/a: not applicable.
[a] Two subjects had HIV-1 RNA ≥50 c/mL at Week 24 but subsequently suppressed to HIV-1 <50 c/mL at a later time point on study without a change in regimen. One subject had no data in the Week 24 window (discontinued due to pregnancy prior to Week 24) but was suppressed at her last visit on study drug.
[b] All subjects with HIV-1 RNA ≥50 c/mL at Week 24 subsequently suppressed to HIV-1 <50 c/mL at a later time point on study without a change in regimen.

Conclusions: In this Week 24 interim analysis of two clinical trials in treatment-naïve adolescents, the E/C/F/TDF and E/C/F/TAF STRs demonstrated efficacy against diverse HIV-1 subtypes with no emergent resistance. E/C/F/TDF and E/C/F/TAF are potentially effective treatment options for HIV-infected adolescent populations globally.

953 Week-24 Data From a Phase 3 Clinical Trial of E/C/F/TAF in HIV-Infected Adolescents

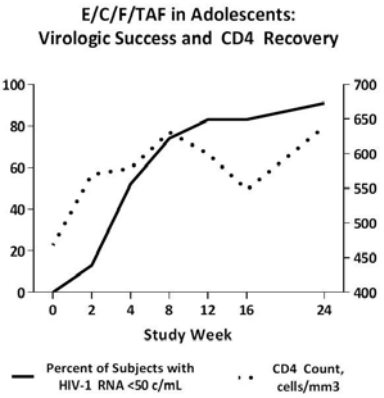
Hilda Kizito[2]; Aditya Gaur[3]; Wasana Prasitsuebsai[4]; Natella Rakhmanina[5]; Eileen Lawson[1]; Yongwu Shao[1]; **Sean R. Bennett**[1]; Andrew Cheng[1]; Erin Quirk[1]

[1]Gilead Sciences, Inc., Foster City, CA, US; [2]Joint Clinical Research Centre, Kampala, Uganda; [3]St Jude Children's Research Hospital, Memphis, TN, US; [4]HIV Netherlands Australia Thailand Research Collaboration, Bangkok, Thailand; [5]Children's National Health System, Washington, DC, US

Background: EVG/COBI/FTC/tenofovir alafenamide (TAF) [E/C/F/TAF] is an integrase inhibitor-based single tablet regimen in clinical development for use in HIV-infected adolescents. Pharmacokinetics, safety and efficacy from a planned interim analysis of the first clinical trial of E/C/F/TAF in adolescents are reported.

Methods: Treatment-naïve 12 to <18 year-olds weighing ≥35 kg with HIV-1 RNA ≥1000 copies/mL (c/mL), CD4 >100 cells/μL and eGFR≥90 mL/min/1.73m^2 received E/C/F/TAF once daily in a prospective, 2-part, 48-week, single-arm, open-label trial. Steady-state pharmacokinetic (PK) parameters were compared to an adult reference population by ANOVA, and related to the range of exposures associated with antiviral activity in adults. Adverse events (AE), laboratory tests, and the proportion of subjects with HIV-1 RNA < 50 c/mL were assessed through Week 24. Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry.

Results: The trial enrolled 48 adolescents with a median age of 15 years, median weight of 52 kg, 58% female, 88% Black, 13% Asian, 67% vertically infected, 35% with HIV-1 RNA > 100,000 c/mL, median CD4 count 468 cells/μL, and median serum creatinine [sCr] 0.57 mg/dL. TAF, TFV, EVG, COBI, and FTC PK profiles of adolescents were consistent with those in adults. Of 23 subjects followed to Week 24, 21 (91%) had HIV-1 RNA <50 c/mL (Figure). No deaths or AE-related discontinuations occurred. The most frequent AEs were nausea (23%), upper respiratory infection (21%), and diarrhea (17%). One serious AE of visual impairment and intermediate uveitis occurred and resolved without interruption of E/C/F/TAF. The median change in sCr was +0.08 mg/dL at Week 24, consistent with cobicistat's inhibition of renal tubular Cr secretion. No renal failure or proximal renal tubulopathy occurred. From baseline to Week 24, the change in median spine BMD was +2.8% with a change in height-adjusted (HA) Z-score of +0.02 and 2/23 subjects (9%) having a decrease of ≥4%. The change in median total body less head BMD was +0.3% with a change in HA Z-score of +0.09 and no decreases of ≥4%. No fractures occurred.



Conclusions: Therapeutic plasma concentrations of all components of E/C/F/TAF were achieved, consistent with potent antiviral activity of the regimen. Treatment was generally well-tolerated through 24 weeks with a favorable renal and bone safety profile. These promising findings support E/C/F/TAF's eventual use in adolescents and its further evaluation in other pediatric populations.

954 Efficacy and Safety of Long-Term Tenofovir DF (TDF) Therapy in HIV-Infected Children

Xavier Saez-Llorens[2]; Jaime G. Deville[3]; Ayesha Mirza[4]; Janet S. Chen[5]; Aditya Gaur[6]; Mobeen Rathore[4]; Dana Hardin[7]; Ya-Pei Liu[1]; **Erin Quirk**[1]
GS-US-104-0352 Study Team

[1]Gilead Sciences, Inc., Foster City, CA, US; [2]Hospital del Niño, Panama City, Panama; [3]University of California Los Angeles, Los Angeles, CA, US; [4]University of Florida, Jacksonville, FL, US; [5]Drexel University College of Medicine, Philadelphia, PA, US; [6]St Jude Children's Research Hospital, Memphis, TN, US; [7]Eli Lilly, Indianapolis, IN, US

Background: Limited long term data are available for pediatric TDF use. We describe preliminary efficacy and safety in HIV-infected children treated with TDF for up to 336 weeks.

Methods: Children ages 2-16 years with HIV-1 RNA <400 copies/mL (c/mL) on a stavudine (d4T)- or zidovudine (ZDV)-containing regimen were randomized to maintain d4T or ZDV or switch to open label (OL) 8 mg/kg TDF oral powder or 300 mg tablets for 48 weeks. Following the randomized phase, subjects in the TDF arm could continue on TDF and those on d4T or ZDV could switch to OL TDF oral powder or tablets at investigator discretion. Subjects maintained their background ARVs for up to 336 weeks in three 96-week study extensions. Safety (adverse events [AE] and laboratories) and efficacy (HIV-1 RNA [Roche Amplicor or Taqman]) were assessed every 12 weeks. Spine and total body less head (TBLH) bone mineral density (BMD) was measured by dual energy X-ray absorptiometry every 24-48 weeks. Proportion with HIV-1 RNA < 50 copies/mL (missing=failure) was assessed. 95% CIs of the point estimate were calculated from the Exact method.

Results: 89 subjects received TDF (49.4% male, median age 7 years, median CD4 1095 cells/mm^3, median CD4% 34). Median TDF duration was 302 weeks. 79 subjects received TDF in OL extensions. Seven discontinued OL TDF for AEs (hypophosphatemia [n=2]; proteinuria [n=2]; brain neoplasm, glycosuria, and arthralgia and hypophosphatemia [n=1 each]). TDF adherence was 95% in 45/89 subjects (50.6%). At Week 336, 32/40 subjects (80.0%; 95% CI 64.4, 90.9%) had HIV-1 RNA <50 c/mL. The most frequent AEs were nasopharyngitis (62.9%), dental caries (23.6%), cough and diarrhea (both 21.3%), and gastroenteritis (20.2%). At Week 336, median change from BL in estimated GFR (Schwartz) was -28.7 mL/min/1.73m^2 (n = 38, BL 166.6 mL/min/1.73m^2) and median BMD percentage change from BL was +43.44% for spine (n=23) and +18.50% for TBLH (n=24). Overall 13/86 subjects (15.1%) had >4% decreases from BL in either spine or TBLH BMD, n=3 at >1 visit.

Table 1: Virologic Response Rates by Visit (Missing=Failure)

	Subjects with <50 c/mL		Subjects with <400 c/mL	
Study Visit	n/N (%)	95% CI	n/N (%)	95% CI
Week 48	61/89 (68.5%)	57.8%, 78.0%	76/89 (85.4%)	76.3%, 92.0%
Week 96	57/79 (72.2%)	60.9%, 81.7%	66/79 (83.5%)	73.5%, 90.9%
Week 144	54/78 (69.2%)	57.8%, 79.2%	63/78 (80.8%)	70.3%, 88.8%
Week 192	53/74 (71.6%)	59.9%, 81.5%	57/74 (77.0%)	65.8%, 86.0%
Week 240	51/71 (71.8%)	59.9%, 81.9%	52/71 (73.2%)	61.4%, 83.1%
Week 288	45/64 (70.3%)	57.6%, 81.1%	47/64 (73.4%)	60.9%, 83.7%
Week 336	32/40 (80.0%)	64.4%, 90.9%	33/40 (82.5%)	67.2%, 92.7%

Conclusions: Most HIV-1 infected children with data available maintained viral responses to TDF-based ARV at Week 336. TDF was well-tolerated. Estimated GFR changes were consistent with increases in age. Few TDF-recipients had persistent BMD decreases. TDF can be considered as a once-daily component of ARV therapy in HIV-infected children.

955 Acceptability of Lopinavir/r Minitabs, Tablets and Syrups in HIV-Infected Children

Adeodata Kekitiinwa
CHAPAS-2

Baylor College of Medicine Children's Foundation Uganda, Kampala, Uganda

Background: LPV/r 'minitabs' provided similar exposure to syrup in the CHAPAS-2 trial. After 12 weeks, they were more acceptable than syrups for young children, but older children preferred tablets. Here we describe acceptability at week 48.

Methods: CHAPAS-2 was a randomised, 2-period crossover trial in HIV-infected infants/children taking first- or second-line ART with 2 NRTIs+LPV/r from 2 clinics ("JCRC", "PIDC") in Uganda. Infants aged 3-<12 months (group A, n=19) started syrup and switched at week 4 to minitabs; children aged 1-4 years (group B, n=26) started minitabs and switched to syrup or vice versa; and children aged 4-<13 years (group C, n=32) started tablets and switched to minitabs or vice versa. At week 8, all groups chose which formulation to continue. Formulation acceptability data were collected at weeks 4, 8, 12, and 48. VL was measured at week 48.

Results: For groups A and B overall, the proportion preferring minitabs increased between weeks 0 and 12 and decreased at week 48 (group A 37%, 72%, 44%; group B 12%, 64% and 36% respectively). However at week 48, group B's preferences differed between JCRC and PIDC: 70% JCRC vs 13% PIDC preferred minitabs. For older children (group C), minitabs were progressively less preferred to tablets over time: 41%, 19%, 13% at weeks 0, 12, 48 respectively.

Formulations taken in the preceding 4 weeks reflected preferences; clinics differed: groups A/B at JCRC more likely to be on minitabs at week 48 (40%/82% JCRC vs 15%/20% PIDC respectively). For group C, 23% and 13% were on minitabs at weeks 12 and 48 respectively.

Unpleasant taste was similarly reported among young children taking minitabs and syrups (37%/43% group A and 29%/26% group B), whereas among older children, minitabs were worse than tablets (40%/2%). There were no reported problems with storage and transportation for minitabs (0%/0% respectively) unlike syrups (23%/13%). Of 19 children with VL assayed at week 48, 14 were <50 c/ml and all were <1000 c/ml.

Conclusions: For infants and young children, minitabs were more acceptable at week 12 but not at week 48. Differences between clinics could reflect bias among healthcare workers for different formulations. Minitabs taste similar to the syrup, are easier to store and transport than syrup bottles, and represent an alternative formulation for young children unable to swallow tablets. Improvements in taste of the current formulation may help sustain acceptability.

956 Therapeutic Drug Monitoring of Lopinavir in HIV-Infected Children on Second-Line ART

Linda Aurpibul[1]; Wasana Prasitsuebsai[2]; Tavitiya Sudjaritruk[3]; Pope Kosalaraksa[4]; Nia Kurniati[6]; Khanh Huu Truong[5]; Viet Chau Do[7]; Sirinya Teeraananchai[2]; Stephen J. Kerr[2]
the TASER-Pediatrics Study Group

[1]Research Institute for Health Sciences, Chaing Mai University, Chiang Mai, Thailand; [2]The HIV Netherlands Australia Thailand Research Collaboration, The Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [3]Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [4]Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand; [5]Children's Hospital 1, Ho Chi Minh City, Viet Nam; [6]Cipto Mangunkusumo General Hospital, Jakarta, Indonesia; [7]Children's Hospital 2, Ho Chi Minh City, Viet Nam

Background: Failure rates of second-line boosted protease inhibitor (PI) regimens in children in resource-limited settings are expected to rise over time. Therapeutic drug monitoring can contribute to assessments of adherence and inform decisions to conduct resistance testing. We assessed the performance characteristics of the US DHHS-

recommended lopinavir (LPV) trough concentration (C_{trough}) of 1mg/L for predicting virologic failure (VF) and intermediate-to-high level LPV resistance in Asian children in a resistance monitoring study of second-line antiretroviral therapy (ART).

Methods: Data from study participants in Indonesia, Thailand, and Vietnam receiving second-line LPV-based ART and followed for ≥24 weeks were analyzed. All had random or trough LPV concentrations and viral load assessments at 24 weeks after enrollment. Those with VF (HIV RNA >1000 copies/mL) had genotypic resistance testing; 46MLI, 47V, 54V, 76V, 82AS, 88S, and 90M were considered major PI mutations. For VF and resistance, we calculated sensitivity, specificity, and area under the receiver operating characteristics curve (AROC) as a measure of correctly predicting outcomes, versus the target LPV level.

Results: The 223 children on LPV had a median age of 10.4 (IQR 7.9-13.4) years; 61% were male. At study enrollment, mean CD4 was 842±438 cells/mm^3, mean HIV RNA was 2.3±0.9 $\log_{10}$ copies/mL, median LPV duration was 2.5 (IQR1.3-4.2) years, and ≥95% adherence was reported by visual analogue scale (VAS) in 200 (90%) and by pill count in 192 (86%). In 84 children with a LPV C_{trough} at week 24, a cut-off at 1 mg/L gave an AROC of 0.82 in predicting VF with sensitivity of 67% and specificity of 96% (Table 1). Of 21 children with VF at study week 24, 7 had major PI mutations (5 with intermediate/high level resistance) but only 1/7 had low LPV C_{trough}. After week 24,14 children had VF and LPV C_{trough} available: 5 (35%) had LPV C_{trough} <1 mg/L, and only 2 with C_{trough} >1mg/L had major PI mutations. Multivariate logistic regression found LPV concentrations <1 mg/L vs. ≥1mg/L (OR 6.47; 95%CI 2.15-19.50, P=0.001) and CD4 ≤20% (OR 2.83; 95%CI 1.01-7.89, P=0.05) were associated with VF; age, duration on LPV, WHO staging, and adherence assessed by pill count or VAS were not. No factors predicted major LPV resistance mutations.

Table 1 Performance characteristics of the DHHS recommended lopinavir concentration of 1mg/L for predicting virologic failure (VF)

Endpoint	LPV concentration	Number of patients	Sensitivity (%)	Specificity (%)	AROC (95%CI)
Virologic failure (HIV RNA > 1000 copies/mL)	Random and trough concentrations	223	44	94	0.69 (0.58 – 0.79)
	Trough concentration	84	67	97	0.82 (0.49 – 1.00)

Conclusions: LPV C_{trough} of 1 mg/L predicted VF, but not the risk of major LPV mutations. Children with LPV concentrations <1mg/L and CD4 ≤20% were at greater risk for VF.

WEDNESDAY, FEBRUARY 25, 2015

Session P-V1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Postexposure Prophylaxis (PEP)

957 Significant Intolerability of Efavirenz in HIV Occupational Postexposure Prophylaxis

Surasak Wiboonchutikul[1]; Varaporn Thientong[1]; Patama Sutha[1]; Boonchai Kowadisaiburana[2]; Weerawat Manosuthi[1]

[1]Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand; [2]Bangkok Hospital, Bangkok, Thailand

Background: Postexposure prophylaxis (PEP) has been used to decrease a risk of HIV transmission after occupational exposure. Regimen completion is one of the most important factors in successful prophylaxis. Limited data are available on tolerability of PEP regimens in healthcare workers (HCWs) in resource-limited settings. We aimed to describe the characteristics of occupational exposure, and sought to determine factors associated with incompletion of the 4-week HIV prophylactic course.

Methods: A retrospective study was conducted among HCWs who accidentally exposed to blood or body fluid of patients at Bamrasnaradura Infectious Diseases Institute, Thailand, between March 1996 and June 2014. The characteristics of exposure were described, and logistic regression analysis was used to determine factors associated with incompletion of the 4-week prophylactic course.

Results: A total of 225 exposure episodes were reported (163 percutaneous injury, 43 mucosal exposure, 6 non-intact skin exposure, and 13 intact skin exposure). The mean (SD) age was 33.1 (9.9) years and 189 (84%) were females. The most frequently exposed groups were nurses (43%), patient or nurse assistants (18%), and medical technicians (15%). The HIV status of the source was defined in 149 (66%) episodes which were positive in 101 (68%). Of 225 exposures, PEP was prescribed in 155 (69%) episodes but was subsequently intentionally discontinued in 26 episodes (HIV source was negative in 19, refusal to continue in 7). PEP courses should have completed in 129 episodes. Of 129 prescribed regimens, 38% were 2 NRTIs, 37% were 2 NRTIs + PIs, 12% were Zidovudine alone, 9% were 2 NRTIs + Efavirenz (EFV), and 4% were 2 NRTIs + Raltegravir. Only 91 of 129 (71%) HCWs were able to complete the 4-week regimen. Multivariate analysis showed that 2 NRTIs + EFV was the only significant factor associated with incompletion of the 4 week-course (OR 33.3; 95% CI 4.2-100; $p < 0.01$). Other factors including age, gender, staff position, status of the source, and other PEP regimens were not associated with incompletion of the 4-week course ($p > 0.05$). The reason for premature discontinuation of 2 NRTIs + EFV was intolerability in all HCWs. None of the HCWs was reported to have HIV seroconversion.

Conclusions: Two NRTIs + EFV regimen was significantly associated with premature discontinuation of occupational PEP. This regimen should not be further used for HIV prophylaxis following occupational exposure in the resource-limited settings.

958 Rilpivirine-Emtricitabine-Tenofovir for HIV Nonoccupational Postexposure Prophylaxis

Rosalind Foster[1]; John McAllister[2]; Tim R. Read[3]; Anna Pierce[4]; Robyn Richardson[2]; Anna McNulty[1]; Andrew Carr[2]
On behalf of the EPEP Study Researchers

[1]Sydney Sexual Health Centre, Sydney, Australia; [2]St Vincent's Centre for Applied Medical Research, Sydney, Australia; [3]Melbourne Sexual Health Centre, Melbourne, Australia; [4]The Alfred Hospital, Melbourne, Australia

Background: CDC recommends 3-drug post-exposure prophylaxis (PEP) with emtricitabine-tenofovir disoproxil fumarate (FTC-TDF) plus raltegravir (RAL) for 28 days. But in one non-occupational (N)PEP study, FTC-TDF-RAL adherence was imperfect (only 52% took all 3 pills/day) and RAL was associated with acute muscle adverse effects (9%). FTC-TDF coformulated with rilpivirine (RPV) as a single-tablet regimen (STR) is a well-tolerated, once-daily NPEP candidate. A plasma tenofovir (TFV) level >40ng/mL is thought to reflect recent full adherence, whereas a level <10ng/mL suggests no dose for ≥7 days. NPEP studies to date have neither evaluated STRs nor measured TFV levels. We hypothesized FTC/RPV/TDF as an STR NPEP would be safe, well-tolerated, and result in high adherence.

Methods: We evaluated NPEP with STR FTC/RPV/TDF for 28 days in gay men after high-risk, sexual exposure, in an open-label, single-arm study. We assessed adherence (pill count; patient report; and plasma TFV levels at Week 4 in a subset by HPLC), adverse events (AEs) and HIV status through Week 12. Final intention-to-treat (ITT) analyses are reported.

Results: 100 men (mean age 31 years [SD 9]) presented a mean 30 hours (SD 21) after anal sex (88% receptive). NPEP commenced 2 hours (SD 2.3) post-presentation. No participant was HIV+ at enrolment or through Week 12, or ceased NPEP because their 'source' was found to be HIV-negative. NPEP completion was 92% (95%CI 85 to 96); failures occurred at median 14 days for loss to follow-up (6%), adverse event (1%) or study burden (1%). NPEP adherence was 98.6% (SD 2.7) by self-report. In the 78 participants with pill-count data, adherence was 98.7% (SD 2.4). 86% reported taking all doses with food. Of 78 paired assessments available for percent adherence by pill count and self-report, agreement was 100% (kappa=1.0; P<0.0001). From the final 50 participants, plasma TFV was measured within 48 hours of the last dose in 41 (88%) participants who reached Day 28 (mean 16 hrs [SD 10]): 36 (88%) participants had levels >40ng/mL and only 1 (2%) was <10ng/mL. One participant developed pancreatitis 1 day post-NPEP. 5 other participants developed a Grade 3 AE; 2 possibly due to study drug**.** Grade 3+ lab AEs possibly due to study drug occurred in 2 participants. Mean serum creatinine rose from 83 to 88 μM/L at Day 28 (P<0.001), but with no grade 1+ increase and no significant change in serum phosphate.

Conclusions: STR FTC/RPV/TDF was well-tolerated as once-daily NPEP, with high levels of adherence and completion.

959 Tenofovir/Emtricitabine Plus LPV/r vs MVC or Raltegravir for PEP: 2 Randomized Trials

Lorna Leal; Agathe Leon; Berta Torres; Alexy Inciarte; Constanza Lucero; Josep Mallolas; Maria Martinez-Rebollar; Ana González-Cordón; Jose M. Gatell; Felipe Garcia

Hospital Clínic Barcelona, Barcelona, Spain

Background: PEP is recommended after a potential exposure to HIV. In animal models, PEP has to be maintained 4 weeks to be effective. However, with the recommended regimens in humans, side effects are frequent and are the main reason for poor adherence and a high rate of discontinuation. The objective of these 2 trials was to assess the rate of discontinuation of PEP at 28 days comparing the standard of care Lopinavir/r (LPV/r) vs Maraviroc (MVC) or Raltegravir (RAL) both with Tenofovir/Emtricitabine **(**TVD).

Methods: Individuals coming to the emergency room (ER) for potential sexual exposure to HIV were randomized to: TVD 200/245 QD plus LPV/r 400/100 BID (n=117) or plus MVC 300 BID (n=120) in one trial (n=237) and TVD plus LPV/r (n=121) or plus RAL 400 BID (n=122) in the second trial (n=243). After randomization, 4 follow-up visits were scheduled: day 0, 28, 90 and 180. The primary end-point was rate of discontinuation at day 28. Secondary end-points were adherence to PEP, side effects and rate of seroconversions.

Results: In MVC and RAL trials, median age was 35 and 33 years and 92% and 90% were males respectively. The median interval between exposure and presentation at ER was 15h and 13.5h. Type of exposition was male homosexual sex in 83% and 81%. The level of risk was high in only 13% and 9% of individuals. The source patient was known to be HIV infected in 30.8% and 31%. In MVC trial, only 187/237 (79%) who were randomized and started PEP attended the first scheduled visit (day 0) and differences between arms were not observed (p=0.92). Similar results were found in RAL trial [198/243 (81.5%) attended the day 0 (p=0.62)]. The rate of discontinuation of PEP before day 28 of follow-up was significantly higher in LPV/r (31.5%) vs MVC (11.6%) arm (p=0.001) and in LPV/r (36.6%) vs RAL (23.7%) arm (p=0.04). The proportion of patients with low adherence to PEP was similar in LPV/r vs MVC arms (54% vs 46%, respectively, p=0.56), but was higher in LPV/r vs RAL arms (49.2% vs 30.8%, respectively, p=0.03). Adverse effects were reported in 122 out of 187 (50.8%) patients in MVC study attending at least the day 0 visit [70/92 (76.1%) in LPV/r and 52/95 (54.7%) in MVC arm, p=0.002] and in in 134 out of 198 (67.7%) patients in RAL study [75/101 (74.3%) in LPV/r and 59/97 (60.8%) in RAL arm, p=0.04]. No seroconversions were observed.

Conclusions: The rate of discontinuation of PEP and side effects were higher in patients allocated to TVD plus LPV/r as compared with those with TVD plus MVC or TVD plus RAL.

960 Effects of Three Regimens of PEP on the Immune System of HIV-Seronegative Individuals

Alberto C. Guardo[1]; Lorna Leal[2]; Agathe Leon[2]; Cristina Rodriguez de Miguel[2]; Manel E. Bargallo[1]; Cristina Rovira[1]; Josep Llach[2]; Jose M. Gatell[2]; Felipe Garcia[2]; Montserrat Plana[1]

[1]L'Institut D'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; [2]Hospital Clinic, Barcelona, Spain

Background: According to studies in animal models, Postexposure Prophylaxis (PEP) has to be maintained 4 weeks to be effective. However, with the diversity of the actual regimens, the consequences of those temporary window treatments at immunological level are not well characterized.

The objective of this pilot study was to assess the immunological effects of antiretroviral therapy during 28 days of PEP comparing the standard of care Lopinavir/r (LPV/r) vs Maraviroc (MVC) or vs Raltegravir (RAL), all of them with Tenofovir/Emtricitabine (TVD).

Methods: Peripheral blood mononuclear cells (PBMCs) and mononuclear cells (MNC) from rectal biopsy specimens were collected from 30 men who have sex with men (MSM) with a potential sexual exposure. All of them were selected from two different PEP randomized clinical trials. Three arms (TVD plus LPV/r (n=9) or plus MVC (n=11) or plus RAL (n=10)) and four follow-up visits were scheduled (day 1, 7, 28 and basal). Flow cytometry was used to measure immune activation (CD38 and HLA-DR), senescence (CD57 and CD28) and CCR5 expression in CD4 and CD8 T cells. Additionally levels of naïve, effector and memory T cells (CCR7 and CD45RA) were also evaluated.

Results: In PBMCs senescence and activation of CD4 T cells improved significantly in RAL arm between basal and day 28 (CD28: 93.5% vs 97.5%, p= 0.02; CD57: 4.8% vs 1.5%, p=0.03; CD38+DR+: 5.8% vs 2.6%, p=0.05, respectively) whereas no changes were observed in the other two regimens. At the same time points MVC arm, increased significantly the expression of CCR5 in both lineages CD4 (4.7% vs 15%, p=0.002) and CD8 (6.3% vs 16.1%, p=0.004) T cells, probably as a consequence of blockade of its internalization. No differences were detected at basal time among arms and only at day 28 was observed that RAL arm reduced significantly the mentioned percentage of CD4+CD38+DR+ in comparison with MVC arm (7.4% vs 2.6%, p=0.02, respectively). Regarding rectal biopsies not significant differences were detected among arms except for a marked increase in the proportion of CD4 naïve T cells in MVC arm (RA+CCR7+:35.8% vs 46%, p=0.03).

Conclusions: The rates of activation and senescence of the immune system were significantly lower in CD4 T cells from individuals on PEP with TVD plus RAL as compared with those with the other two regimens. Although these data should be confirmed due the low number of patients, our findings in combination with the results of better adherence and tolerance strongly support RAL regimens for PEP.

961 Management of Acute HIV After Initiation of Postexposure Prophylaxis: Challenges and Lessons Learnt

Goli Haidari[1]; Naomi Fitzgerald[4]; Sonia Raffe[2]; Nneka Nwokolo[3]; Olamide Dosekun[1]; Mark D. Lawton[5]; Nickie Mackie[1]; Julie Fox[4]; Martin Fisher[2]; Sarah Fidler[1]

[1]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom; [2]Brighton and Sussex Hospitals NHS Trust, Brighton, United Kingdom; [3]Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom; [4]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [5]The Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, United Kingdom; [6]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom; [7]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [8]Brighton and Sussex Hospitals NHS Trust, Brighton, United Kingdom; [9]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom

Background: International guidelines recommend HIV post exposure prophylaxis following sexual exposure (PEPSE) to prevent HIV infection. However, methods to screen for infection prior to initiating PEPSE are less clear, with little or no guidance for management of acute HIV diagnosed during PEPSE. We present a case series of individuals diagnosed HIV+ whilst on PEPSE.

Methods: Cases definitions include the following criteria:

1. PEPSE failure: negative point of care test (POCT) and 4th generation laboratory test at PEP start, with HIV diagnosed during PEP or in follow up period

2. Acute HIV infection at PEPSE initiation: negative POCT but subsequent reactive 4th generation test at PEP start

Results: 18 patients identified; 17 male/1 female, mean age 34 years. 11/18 (67%) had a previous negative HIV test using laboratory Abbott Ab/Ag tests, 1/18 POCT, in the preceding 12 months to accessing PEP. 18/18 were prescribed NRTI + bPI, 16 of these in line with current UK guidelines.

From data available on 16 (2 not diagnosed at our trusts), HIV diagnoses were subsequently made using laboratory Ab/Ag test in 14/16, POCT in 1 and HIV RNA in 1. 1/18 tested negative by POCT and Ab/Ag lab tests at PEP start, subsequently tested HIV+ with a weakly reactive p24 antigen and positive HIV-RNA on laboratory testing 19 days after completing a 28 day PEP course. The remaining 17 patients initiated PEP based on a negative POCT or recent negative HIV antibody test but were subsequently diagnosed HIV+ using lab tests . Therefore 17/18 (94%) of patients were already HIV+ at PEP initiation.

Of those diagnosed HIV+ whilst still on PEP, 11/16 (68%) opted to continue ART. A decision was made to stop PEP in 5 patients (mean number of days on PEP; 10); this advice was not influenced by CD4 or HIV RNA. 5/11 switched PEP regimes to first line ART. 2/18 had drug resistance: K103N, T215D at diagnosis.

Conclusions: Patients presenting for PEP after sexual exposure are high-risk individuals who may be seroconverting at the time of presentation. It is essential that if a POCT is used at screening, this is accompanied by a 4th generation test as near to initiation as possible, and that dual therapy (as still recommended in some guidelines) must be avoided in this setting.

Acute HIV diagnosis whilst on PEP represents an opportunity for early ART with reduction of viral reservoirs and improvements in CD4 outcome. In the absence of specific data to inform best practice, we recommend continued ART until urgent review by an HIV specialist.

THURSDAY, FEBRUARY 26, 2015

Session P-V2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

PrEP and Microbicide Challenge

962 FTC/TDF Prevents SHIV Infection in *C trachomatis* and *T vaginalis*-Infected Macaques

Jessica Radzio; Tara Henning; James Mitchell; Angela Holder; Debra Hanson; Janet McNicholl; Walid Heneine; John Papp; Ellen Kersh; Gerardo Garcia-Lerma

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: Genital tract inflammation associated with pre-existing sexually transmitted infections (STIs) can increase HIV risk and potentially reduce the efficacy of pre-exposure prophylaxis (PrEP) for HIV prevention. We used a pigtail macaque model of co-infection with *Chlamydia trachomatis* and *Trichomonas vaginalis* to investigate if cervicovaginal inflammation due to STIs can decrease the prophylactic efficacy of oral tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). Additionally, we evaluated the effect of the STIs on dATP and dCTP concentrations in vaginal tissues.

Methods: Eleven female pigtail macaques were inoculated with *C trachomatis* (serovars D and E) and *T vaginalis* (strain Balt 42) and exposed vaginally to SHIV once a week for up to 16 weeks. Macaques received placebo (n=5) or FTC/TDF (n=6) 24h before and 2h after each weekly SHIV exposure. *C trachomatis* and *T vaginalis* infections were maintained with boosting doses given every 3 to 4 weeks, and were monitored weekly by APTIMA testing. The impact of STIs on dATP and dCTP levels in vaginal tissues was evaluated using biopsy specimens collected from 5 additional macaques 1-3 weeks after STI inoculations. TFV-DP, FTC-TP, dATP, and dCTP levels were measured by HPLC.

Results: APTIMA results for *C. trachomatis* and *T. vaginalis* were positive in 87% and 81% of vaginal swabs, respectively, demonstrating maintenance of both STIs during the study. All 5 placebo controls were infected with SHIV after a median of 2 (range=2-5) challenges. In contrast, 4 of 6 PrEP-treated animals remained uninfected after 16 challenges ($p<0.01$). TFV-DP and FTC-TP levels in PBMCs at the estimated week of infection in the 2 PrEP failures (13 and 31 fmols of TFV-DP and 168 and 188 fmols of FTC-TP per 10^6 cells) were similar to those in the 4 protected macaques (14 to 22 fmols TFV-DP and 160 to 318 fmols FTC/10^6 cells), as were TFV-DP/dATP and FTC-TP/dCTP ratios ($p>0.5$). *C. trachomatis* and *T. vaginalis* infection increased dATP and dCTP levels in vaginal tissues (15 to 32 fmols/mg for dATP, and 3.4 to 9.8 fmols/mg for dCTP; $p<0.02$).

Conclusions: Oral FTC/TDF maintains prophylactic efficacy in a macaque model of prolonged co-STI infection, although the infection of 2 macaques that had protective drug levels signals a modest loss of PrEP activity due to STIs. Increases in vaginal dATP and dCTP levels post-STI likely reflects increased cellular activation and may potentially modulate the efficacy of PrEP by increasing competition with tenofovir and FTC.

963 Impact of Sexually Transmitted Infections on the Efficacy of Tenofovir Vaginal Gel in Macaques

Natalia Makarova; Tara Henning; Andrew Taylor; Chuong Dinh; Carol Farshy; Janet McNicholl; John Papp; Walid Heneine; Ellen Kersh; **Charles W. Dobard**

US Centers for Disease Control and Prevention, Atlanta, GA, US

Background: Sexually transmitted infections (STI) increase risk of HIV acquisition in women and can potentially diminish efficacy of PrEP, particularly for vaginal gels that rely mainly on local protection of the vaginal mucosa. Here, we used a macaque model of STIs to evaluate if the protective efficacy of vaginal TFV gel is reduced in the presence of STIs. In this model, pigtail macaques co-infected with *Chlamydia trachomatis* (*CT*) and *Trichomonas vaginalis* (*TV*) show increased susceptibility to SHIV infection and reproduce the cervicovaginal inflammation documented in women. We additionally assessed the impact of the STIs on vaginal drug absorption.

Methods: Female pigtail macaques (n=10) were inoculated vaginally with *CT* (serovars D and E) and *TV* (strain Balt 42) and exposed twice-weekly to SHIV162p3 (50 TCID) for up to 10 weeks. STI infections were sustained with boost inoculations given every 3 weeks and were monitored weekly by APTIMA testing. Macaques received placebo (n=4) or 1% TFV gel (n=6) 30 minutes before each SHIV exposure. SHIV infection was monitored by serology and plasma virus load by RT-PCR. Vaginal absorption of TFV from gels was evaluated longitudinally by measuring TFV in plasma by HPLC MS/MS.

Results: APTIMA results for *CT* and *TV* were positive in 78% and 86% of all vaginal swabs collected, respectively, demonstrating that the dual infections were maintained during the challenge study. All macaques receiving placebo gel were SHIV-infected after a median of 4 weeks (7 challenges). In contrast, all 6 TFV gel-treated animals remained uninfected after 10 weeks (20 challenges), demonstrating that TFV gel maintained complete protection in the presence of STIs. The Tmax for peak TFV levels in plasma after vaginal gel dosing was 30 min. Longitudinal assessment of plasma drug levels revealed peak TFV absorption at Tmax was significantly higher in macaques with STIs compared to non-STI animals (median = 76.64 ± 10.70 and 29.10 ± 3.198 ng/ml, respectively; $p<0.0001$).

Conclusions: In this model, vaginal TFV gel maintained complete protection against SHIV infection in the setting of STI co-infection. The trend for higher TFV concentrations in plasma of STI co-infected than in non-STI animals may reflect higher tissue permeability and drug loading. Both the modest increase in susceptibility by STIs and the high mucosal drug exposures following vaginal gel dosing, likely explain the observed protection by TFV gel.

964 Oral Single-Dose Maraviroc Does Not Prevent Ex Vivo HIV Infection of Rectal Mucosa in Healthy HIV-1–Negative Human Volunteers in Tissue Explants.

Josep Coll[2]; José Moltó[2]; Jaume Boix[3]; Laura Else[4]; Elisabet Garcia[1]; Roger Paredes[2]; David Back[4]; Bonaventura Clotet[5]; **Cecilia Cabrera**[1]

[1]Institut de Recerca de la Sida IrsiCaixa, Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol, Barcelona, Spain; [2]Fundació Lluita Contra la SIDA, Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol, Barcelona, Spain; [3]Unidad de Endoscopia Digestiva. Hospital Universitario Germans Trias i Pujol, Barcelona, Spain; [4]Pharmacology Research Laboratories, Liverpool, United Kingdom; [5]Fundació Lluita Contra la SIDA-IRSICAIXA, VIC-UCC (Universitat de Vic-Universitat Central de Catalunya), Barcelona, Spain

Background: Maraviroc (MVC) is a potential candidate for pre-exposure prophylaxis (PreP). We have explored the efficacy of an oral single-dose of MVC to prevent ex vivo HIV infection.

Methods: Ten HIV-negative, healthy male volunteers were enrolled in this study. Rectal infection with *C. trachomatis* or *N. gonorrhoeae* as well as infection with *T. pallidum*, HBV, HCV and HIV-1 were ruled out. Participants received a witnessed single oral dose of MVC (300 mg in 6 and 600 mg in 2 volunteers) on day 7 after enrollment. Rectal biopsies (16-20 per session) were performed at baseline (without MVC) and at day 7 (4 hours after MVC dosing). Additionally, 2 individuals received tenofovir/emtricitabine 300/200 mg qd within 10 days before the rectal biopsy, as a control group. Rectal tissue was incubated with a R5 isolate ($6x10^4$ $TCID_{50}$) for 1h at 370C and washed before transferring onto gelfoam rafts. Culture medium was collected and replaced every 2 days during 18 days and the p24 production was measured. Three replicates were performed for each infection to account for differences in cellularity between biopsies. MVC concentration was measured in plasma and in rectal tissue by validated LC-MS/MS, and normalized to the 300 mg dose.

Results: Overall, MVC was well tolerated and there were no serious adverse events during the study. Median dose-normalized concentration of MVC in plasma and in rectal tissue was 155 ng/mL and 561 ng/mL (p= 0.0006). Despite MVC concentrations in rectum being above the IC_{50} reported in colorectal tissue infections (56.4 ng/mL), *ex-vivo* HIV infection occurred in all participants specimens, both at baseline and at day 7, even after administration of double MVC dose. Conversely, a complete inhibition of the infection was observed in cultures from the two volunteers who received Truvada.

Conclusions: In our experimental model, a single oral dose of MVC 300 mg or 600 mg did not prevent *ex vivo* infection of human rectal mucosa 4 hours after dosing, even though the drug concentration achieved in tissue was above the IC_{50} reported in rectal tissue. The lack of prophylactic efficacy observed in our study suggests that MVC could not prevent rectal HIV transmission when used as a "on demand" pre-exposure prophylaxis strategy.

965 CCR5 Blockade With Maraviroc Does Not Prevent SIVmac Oral Transmission to Macaques

Egidio Brocca-Cofano[1]; Cuiling Xu[1]; Dongzhu Ma[1]; Benjamin Policicchio[1]; Kevin Raehtz[1]; Tammy Dunsmore[1]; George Richter-Haret[1]; Brandon F. Keele[2]; Ivona Pandrea[1]; Cristian Apetrei[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]National Cancer Institute (NCI), Frederick, MD, US

Background: HIV maternal-to-infant-transmission (MTIT) accounts for >300,000 cases of infection annually. Current prevention strategies cannot eliminate MTIT, and new prevention paradigms are badly needed. We reported that the availability of SIV target cell (i.e., $CCR5^+$ $CD4^+$ T cells) availability at mucosal sites may drive virus transmission efficacy in natural hosts of SIVs, particularly during MTIT. Our goal was to investigate if CCR5 blockade with Maraviroc (MVC) impacts the efficacy of oral SIV transmission to infant rhesus macaques (RMs).

Methods: Nine RMs aged six months were included. Five received MVC (150 mg/kg, bid, orally) for up to 6 months, during which coreceptor occupancy was closely monitored. After one month, treated infant RMs and 4 untreated controls were orally exposed to 10,000 TCID50 of SIVmac766XII (a mixture of 12 barcoded SIVmac251 transmitted/founder clones) every two weeks, for up to 6 times. Plasma viral loads were monitored by real-time single genome amplification. Changes in the immune cells were monitored by flow cytometry.

Results: Coreceptor occupancy testing revealed that MVC effectively blocked CCR5 expression in infant RMs. MVC was well tolerated, with no adverse reaction. At the end of the study, all infant RMs in the control group (4/4) and 60% of those receiving MVC (3/5) became infected with SIVmac766XII, the difference being not significant. There were no differences in the number of exposures needed to infect infant RMs in the two groups (1, 3, 5 and 6 inoculations for controls *versus* 2,3 and 4 inoculation for the RMs receiving MVC). None of the treated or control infant RMs were infected with more than one viral variant, suggesting that the animals were not overexposed to virus, which might have offset the protective effect of MVC. The only difference observed between the two groups consisted of a significant delay of ramp-up viremia in the MVC-treated infants. However, peak and postpeak VLs were similar in the two groups. No significant differences in $CD4^+$ T cells or in the levels of immune activation were observed between the two groups.

Conclusions: MVC was efficient in blocking CCR5 and was well tolerated in infant RMs. Blocking CCR5 with MVC does not significantly impact SIV oral transmission. Since SIVmac is more promiscuous than HIV-1 with regard to coreceptor usage (i.e., being able to use alternative coreceptors, such as BOB/GPR15 and Bonzo/STRL33), CCR5 blockade in humans might be more effective in preventing MTIT.

966LB Correlation of In Vivo Cabotegravir Concentration and Prevention of SIV in Macaques

William R. Spreen[4]; Anabel Lowry[1]; Ranajit Pal[2]; Yun Lan Yueh[4]; Susan Ford[4]; Nicola Richardson-Harman[3]; Jim A. Turpin[1]; Fulvia Veronese[1]; **James E. Cummins**[1]
ABL/BIOQUAL NHP Team

[1]National Institutes of Health, Bethesda, MD, US; [2]Advanced Bioscience Laboratories, Inc, Rockville, MD, US; [3]Alpha StatConsult LLC, Damascus, MD, US; [4]GlaxoSmithKline, Durham, NC, US

Background: Previous studies with long-acting cabotegravir (CAB LA, GSK1265744) demonstrated protection against repeated intrarectal and intravaginal $SHIV_{162p3}$ challenges in nonhuman primates. In one study, evaluation of the "window of protection" was performed using a single dose level of CAB LA in male macaques undergoing repeated intrarectal $SHIV_{162p3}$ challenges. In order to determine if there is a relationship between the plasma drug concentration (as related to Protein Adjusted IC_{90}, PA-IC_{90}) and protection against intravaginal SIV transmission, we assessed plasma PK and longitudinal breakthrough infections in rhesus macaques following multi-exposure intravaginal challenge.

Methods: Twenty-seven Chinese rhesus macaques were injected intramuscularly with CAB LA at three dose levels (10, 30, and 50 mg/kg; n=9) at days -7 and -1 prior to initiation of weekly intravaginal SIV_{mac251} challenges (1000 $TCID_{50}$). Nine untreated (i.e., no CAB LA injection) macaques served as virus controls. Macaques resisting infection after each weekly exposure were continually challenged for a maximum of 20 times and monitored for breakthrough infections. Plasma drug concentration measured by mass spectrophotometry and viral load measured by NASBA were monitored weekly until infection and then for an additional 16 weeks post infection.

Results: Significant protection from virus acquisition was noted in macaques dosed with 30 and 50 mg/kg CAB LA with a median of 9-11 challenges required for infection of drug-treated macaques compared to 3 (2-4 inter-quartile range) for untreated controls ($P<0.05$; Log rank analysis)**.** There were no statistical differences between the 30 and 50 mg/kg doses for protection from infection or between the 10 mg/kg dose (median of 4 protected challenges) and the untreated controls. Analysis of plasma drug concentrations demonstrated a significant correlation between plasma CAB LA concentration and virus acquisition ($P=0.0004$). A CAB LA plasma concentration of 711 ng/mL (~4x PA-IC_{90}) was predicted by logistic regression analysis to provide a 90% probability of *in vivo* protection after 7 SIV challenges.

Conclusions: These results may further elucidate the "window of protection" for cabotegravir and suggest that targeting 4x PA-IC_{90} in plasma may be sufficient to protect against vaginal SIV transmission in macaques, thus supporting a relationship between plasma drug concentration and *in vivo* efficacy.

967 MZC Gel Inhibits Ex Vivo HIV-1 and HSV-2 Infection in Human Cervical Mucosa

Guillermo Villegas; Giulia Calenda; Patrick Barnable; Keith Levendosky; Michael Cooney; José Fernández-Romero; Thomas Zydowsky; Natalia Teleshova
Population Council, New York, NY, US

Background: The transmission of HIV-1 is increased in the presence of other STIs. Of all ulcerative STIs, HSV-2 most strongly impacts sexual transmission and acquisition of HIV. Microbicide products that protect women against HIV and HSV-2 would make a major contribution to public health globally. The Population Council's leading microbicide gel (MZC) containing 50μM MIV-150 (M), 14mM Zinc acetate and Carrageenan (CG) protects against SHIV-RT infection vaginally for up to 8h and rectally for 1h. This study aimed to test activity of MZC against HIV-1/HSV-2 co-infection in human cervical explants.

Methods: HIV-1_{BaL} stock was prepared in the presence of 10μM retinoic acid and 20U/ml of IL-2 in human PBMCs (RA HIV-1_{BaL}). Non-stimulated human ectocervical explants were challenged with 500 $TCID_{50}$ RA HIV-1_{BaL} or co-challenged with 500 $TCID_{50}$ RA HIV-1_{BaL} and 10^6 pfu HSV-2 per explant for ~18h. The viral challenge was performed in the presence of 1:100 and 1:300 diluted MZC (vs. untreated medium, diluted CG and 3TC/Acyclovir controls). The tissues were washed after the ~18h incubation and cultured for 14d. Infections were monitored by one step HIV *gag* RT-qPCR and HSV-2 *pol q*PCR on culture supernatants. SOFT and CUM endpoint analyses were performed. Tissue viability post exposure to diluted gels was tested using MTT assay. Log-normal generalized linear mixed models were used for data analysis.

Results: Tissue challenge with RA HIV-1_{BaL} and HSV-2 resulted in robust infection of non-stimulated tissue with both viruses (single RA HIV-1_{BaL} challenge and co-challenge). MZC (1:100 and 1:300 dilutions) significantly inhibited RA HIV-1_{BaL} infection (vs. medium control) in the single challenge and in the co-challenge models ($p<0.0001$ and $p<0.001$, respectively). RA HIV-1_{BaL} infection level decreased in CG treated tissues (vs. medium control) probably due to a barrier effect (only single challenge; $p<0.001$ for 1:100 dilution only). Both MZC and CG gels (1:100) strongly inhibited HSV-2. The gel formulations did not decrease tissue viability.

Conclusions: MZC is active against RA HIV-1_{BaL} in the single challenge model and under stringent conditions of co-challenge with HSV-2 in human ectocervical mucosa. MZC provides CG-mediated activity against high dose HSV-2 challenge. These results highlight the promise for further development of MZC as a microbicide and support the ongoing Phase 1 testing of vaginal MZC.

968 GRFT/Carrageenan Gel Inhibits SHIV-RT and HSV-2 Infection in Macaque Vaginal Mucosa

Giulia Calenda[1]; Patrick Barnable[1]; Keith Levendosky[1]; Kyle Kleinbeck[1]; Agegnehu Gettie[2]; James Blanchard[4]; José Fernández-Romero[1]; Barry O'Keefe[3]; Thomas Zydowsky[1]; Natalia Teleshova[1]
[1]Population Council, New York, NY, US; [2]Aaron Diamond AIDS Research Center, New York, NY, US; [3]National Cancer Institute (NCI), Fredrick, MD, US; [4]Tulane University, Covington, LA, US

Background: Griffithsin (GRFT) is a lectin with broad antiviral activity, including anti-HIV and anti-HSV-2 activities. The antiviral properties and excellent safety profile have favored GRFT for development as a potential microbicide to prevent HIV/HSV-2 acquisition. Here we tested the safety and antiviral activity of GRFT against *ex vivo* cell-free SHIV-RT, SHIV-RT/HSV-2 co-challenge and cell-associated SHIV-RT in macaque vaginal mucosa.

Methods: Unformulated GRFT and 0.1% **G**RFT formulated in **C**arrageenan (**GC**) were tested (vs. medium and carrageenan (C) alone) in macaque vaginal explants. PHA/IL-2 stimulated explants were co-challenged with 10^4 $TCID_{50}$ SHIV-RT and 10^6 pfu HSV-2 or SHIV-RT only for ~18h in the presence GC diluted 1:100-1:300 (3.93-1.31 μM GRFT) or unformulated GRFT (0.0001-10 μM) or tissues were challenged up to 4d post gel/API washout. Alternatively, SHIV-RT-infected PBMCs (10^3 cells/explant) were used as virus inoculum in a cell-associated challenge model. The tissues were washed, cultured for 14d and infections were monitored by SIV *gag* one step RT-qPCR and HSV-2 *pol* PCR. SOFT and CUM endpoint analyses were performed. Tissue viability post exposure to unformulated GRFT and neat/diluted gels was tested (MTT). Tissue integrity was examined post neat gel exposure (H&E staining). Log-normal linear generalized mixed models were used for analysis.

Results: 0.1-10 μM and 1-10 μM GRFT inhibited SHIV-RT when present at the time of single SHIV-RT challenge and 24h post API washout ($p<0.01$). GC (up to 1:300 dilution) present at the time of co-challenge inhibited SHIV-RT ($p<0.0001$ vs. medium control and CG). GC (1:100) inhibited SHIV-RT when tissues were co-challenged up to 4d post gel exposure ($p<0.01$). GC and C (1:100) present at the time of viral co-challenge (but not post wash out) inhibited HSV-2 ($p<0.01$). 0.1-10 μM GRFT and GC (1:300) present at the time of challenge strongly inhibited cell-associated SHIV-RT infection. The unformulated and formulated GRFT were equally effective against SHIV-RT. No histopathological changes and no decreased tissue viability were detected post gel/API exposure.

Conclusions: GRFT and GC are highly effective against SHIV-RT and provide post washout activity for 24h and up to 4d, respectively. GRFT and GC are highly effective against cell-associated SHIV-RT. Anti-HSV-2 activity of GC was mediated by the carrageenan component. Our data support the notion that GRFT is a strong microbicide candidate for further advancement.

TUESDAY, FEBRUARY 24, 2015

Session P-V3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

PrEP: Uptake

969 Sustained PrEP Use Among High-Risk African HIV Serodiscordant Couples Participating in a PrEP Demonstration Project

Renee Heffron[1]; Kenneth Ngure[2]; Nulu Bulya Semiyaga[3]; Josephine Odoyo[4]; Edna Tindimwebwa[5]; Jennifer Morton[1]; Lara Kidoguchi[1]; Mark A. Marzinke[6]; Connie Celum[1]; Jared Baeten[1]
Partners Demonstration Project Team
[1]University of Washington, Seattle, WA, US; [2]Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya; [3]Makerere University College of Health Sciences, Kampala, Uganda; [4]Kenya Medical Research Institute, Nairobi, Kenya; [5]Kabwohe Clinic Research Center, Kabwohe, Uganda; [6]Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: Pre-exposure prophylaxis (PrEP) demonstrated high efficacy for HIV prevention in a clinical trial among heterosexual African HIV serodiscordant couples. Assessing uptake and sustained use of PrEP outside of clinical trial settings is an important next step for PrEP implementation.

Methods: Between November 2012 and August 2014, high-risk HIV serodiscordant couples were enrolled into an open-label study delivering PrEP and antiretroviral therapy (ART) for HIV prevention in Kenya and Uganda, the Partners Demonstration Project. Quarterly follow up for up to 2 years is ongoing. PrEP is offered to all couples prior to and during the first 6 months after ART initiation by the HIV infected partner, at which time PrEP discontinuation is recommended. Pharmacy refill data and, in a subset, detection of tenofovir in plasma were used to quantify continued use of PrEP.

Results: Two-thirds of couples have HIV-uninfected male partners, the median age of HIV-uninfected partners is 30 years (interquartile range: 26-36), and 65% of couples reported unprotected sex in the month prior to enrollment. Overall, 95% initiated PrEP at enrollment and 97% of those attended their first follow-up visit one month after enrolling and continued to use PrEP. For those still in follow-up at 6 and 12 months after enrollment, and for whom the HIV-infected partner had not initiated ART, 91% and 84%

continued to use PrEP. For those not on PrEP 12 months after enrollment, the most frequent reasons included ART use by the HIV-infected partner (41%), loss to follow-up (30%), pregnancy and breastfeeding (9%), participant preference (8%), and partnership dissolution (6%). Tenofovir was detected in plasma at 86% of 168 visits from 74 randomly-selected participants receiving PrEP.

Conclusions: In a demonstration project among high-risk HIV serodiscordant African couples, PrEP initiation was high. For most participants who chose to start PrEP, use was sustained while there was ongoing HIV risk.

970 PrEP Engagement for HIV Prevention: Results From the iPrEx Open Label Extension (OLE)

David V. Glidden[6]; Susan P. Buchbinder[1]; Peter L. Anderson[2]; Vanessa McMahan[3]; K. Rivet Amico[4]; Albert Liu[1]; Sybil Hosek[5]; Megha Mehrotra[6]; Robert M. Grant[3]
iPrEx Investigators

[1]San Francisco Department of Public Health, San Francisco, CA, US; [2]University of Colorado, Denver, CO, US; [3]Gladstone Institute, San Francisco, CA, US; [4]University of Michigan, Ann Arbor, MI, US; [5]John Stronger Hospital, Chicago, IL, US; [6]University of California San Francisco, San Francisco, CA, US

Background: Pre-exposure prophylaxis (PrEP) with FTC/TDF is a biologically potent strategy for interrupting HIV transmission. PrEP requires a chain of engagement termed the "prevention cascade" — seeking services, initiating FTC/TDF, HIV testing, medication refills and adequate adherence. We characterize this spectrum and identify potential predictors of engagement in the iPrEx OLE study.

Methods: iPrEx OLE examined open-label PrEP uptake and adherence by enrolling men who have sex with men and transgender women at 11 sites in 6 countries and offering up to 18 months of open label FTC/TDF to HIV- former participants in 3 PrEP trials. They were followed quarterly with HIV testing and medical assessments regardless of whether they elected to receive PrEP. Exposure to FTC/TDF used a case/cohort design to test for TFV-DP in dried blood spots (DBS) collected for all on-PrEP seroconverters (n=28) and a randomly selected sample (n=325, 27%) of the cohort. iPrEx OLE showed TFV-DP levels ≧ 700 fmol/punch (consistent with ≧ 4 pills per week) as highly protective against HIV infection. Predictors of a DBS levels of ≧ 700 fmol/punch were assessed in a probability weighted multivariable logistic regression model.

Results: Of 1603 HIV- participants, 1125 (76%) initiated PrEP. At the 12 month visit after starting PrEP, 1005 of initiators (84%) attended, 813 had been dispensed PrEP at the last visit, and an estimated 354 had TFV-DP levels ≧ 700 fmol/punch, yielding highly protective concentrations at 12 months in 22% of those offered PrEP. These percentages were 34% at 3 months and 26% at 6 months. TFV-DP levels ≧ 700 fmol/punch at 12 months varied by site ($p < 0.001$) ranging from 11% to 63% of those offered PrEP. Percentages were higher among those reporting non-condom insertive anal intercourse (nclAI) (p=0.02), a diagnosed sexual transmitted infection (p=0.046), a HIV+ partner (p=0.02), and secondary (p=0.03) or higher ($P< 0.001$) education. No significant differences were observed by transgender identity, age, non-condom receptive anal intercourse or drug use

	% of HIV-Participants	% ≥ 700 fmol/punch at 12 months	P-value
Non Condom Insertive Anal Intercourse at Entry			
No	76%	19%	Ref.
Yes	24%	29%	P=0.02
Non Condom Receptive Anal Intercourse at Entry			
No	68%	20%	Ref.
Yes	32%	25%	P=0.12
HIV+ Partner Reported at Entry			
No	89%	20%	Ref
Yes	11%	33%	P=0.02
Highest Education			
Less than Secondary	21%	10%	Ref.
Secondary	52%	19%	P=0.03
Post-Secondary	27%	33%	P < 0.001
HSV/Syphilis/Chlamydia/Gonorrhea at Entry			
No	46%	18%	Ref.
Yes	54%	25%	P=0.046

* Adjusted percentages from a probability weighted multivariate logistic regression

Conclusions: There are challenges across the prevention cascade in uptake of PrEP, as well as engagement with and adherence to PrEP. Less than half of participants who attended study visits and were dispensed medication had TFV-DP levels consistent with ≧ 4 pills per week. Prevention engagement was higher among participants with secondary education, a HIV+ positive partner, a sexually transmitted infection, and nclAI.

971 Preliminary Follow-up of Injecting Drug Users Receiving Preexposure Prophylaxis

Michael T. Martin[1]; Suphak Vanichseni[2]; Pravan Suntharasamai[2]; Udomsak Sangkum[2]; Philip Mock[1]; Manoj Leethochawalit[3]; Sithisat Chiamwongpaet[3]; Somyot Kittimunkong[4]; Marcel Curlin[1]; Kachit Choopanya[2]

[1]US Centers for Disease Control and Prevention (CDC), Nonthaburi, Thailand; [2]Bangkok Tenofovir Study Group, Bangkok, Thailand; [3]Bangkok Metropolitan Administration, Bangkok, Thailand; [4]Ministry of Public Health, Nonthaburi, Thailand

Background: The Bangkok Tenofovir Study (BTS) was a randomized, double-blind, placebo-controlled, HIV pre-exposure prophylaxis (PrEP) trial, conducted among people who inject drugs (PWID) in Bangkok 2005-2012. The trial demonstrated that taking tenofovir daily can reduce the risk of HIV infection 49% among PWID. Following the announcement of trial results, study participants were offered one year of open label tenofovir. We present demographic characteristics, risk behavior, and preliminary follow-up data from participants who chose to take daily open label tenofovir.

Methods: BTS participants were offered tenofovir, free of charge, at 17 drug treatment clinics in Bangkok. Participant demographics and risk behaviors were assessed, using audio-computer-assisted self-interview, at baseline and every 3 months. HIV testing was done monthly and serum creatinine testing every 3 months.

Results: From August 2013 through May 2014, 787 (35%) of 2254 surviving HIV-uninfected BTS participants chose to start taking tenofovir; 236 (30%) have completed 12 months follow-up. The median age of the 787 participants was 39 years, 631 (80%) were male, 394 (50%) had completed primary school or less education, and 128 (16%) were in prison. Risk behavior data were available for 718 (91%) participants; 149 (21%) reported injecting drugs during the 3 months before enrollment: 87 (58%) injected midazolam, 58 (39%) injected heroin, and 48 (32%) injected methamphetamine; 17 (11%) reported sharing needles. Based on summary data from participant adherence diaries, 26% of participants have missed ≤8 days in the most recent 28 days of follow-up. One participant has become HIV-infected after starting PrEP yielding an estimated HIV incidence of 3.3 (95% CI,

0.1-18.6) per 1000 person-years. HIV incidence among BTS placebo recipients in the 2005-2012 trial was 6.8 (95% CI, 4.7-9.6) per 1000 person-years and among tenofovir recipients was 3.5 (95% CI, 2.1-5.6) per 1000 person-years.

Conclusions: Bangkok Tenofovir Study open label follow-up has begun and 35% of eligible participants have decided to take daily tenofovir. HIV incidence among participants who have chosen to take daily tenofovir is similar to the incidence in the tenofovir group during the 2005-2012 trial. Only 26% of open label participants are consistently coming to the clinics to take PrEP suggesting additional adherence support is needed.

972 Recent Increases in PrEP Utilization at a Boston Community Health Center Among Men Who Have Sex With Men, 2011-2014: Transition From Research to Clinical Practice

Kenneth H. Mayer[1]; Kenneth Levine[1]; Chris Grasso[1]; Douglas S. Krakower[1]; Matthew Mimiaga[2]

[1]Fenway Health, Boston, MA, US; [2]Harvard School of Public Health, Boston, MA, US

Background: Although pre-exposure prophylaxis (PrEP) has been recommended by the CDC to prevent HIV transmission among men who have sex with men (MSM) and heterosexuals who engage in condomless sex with HIV-infected and/or high risk partners, prior reports have suggested low uptake by key US populations.

Methods: Fenway Health (FH), a Boston community health center which has specialized in sexual and gender minority primary care since 1971 has used an electronic medical record (EMR) to document clinical encounters since 1997. EMRs of HIV-uninfected patients who were prescribed Tenofovir/Emtricitabine for more than one month were reviewed. Time trend analyses were calculated to examine the presence of upward trends for: 1) the total number of PrEP prescriptions, annually, from 2011 to 2014, 2) ethnic/racial diversity, and 3) age distributions of PrEP users.

Results: Six patients (pts) were prescribed PrEP in 2011; 23 in 2012; 104 in 2013; 326 by 9/20/2014 (upward trend; $p<0.05$). Although all pts who were prescribed PrEP were White in 2011, by 2014, 8.8% of PrEP users were Black pts and 20.9% were from other racial or ethnic groups (upward trend; $p<0.05$). In 2011, 50% of PrEP users were < 30 years old (y.o.); in 2014, 40.5% of PrEP users were <30 y.o. Almost all PrEP users were MSM, with only 1 heterosexual man, 2 women and 16 transgender persons being prescribed PrEP at FH since 2011. Over 4/5 (84.1%) of prescriptions were covered by commercial insurance, with 5.0% covered by Medicare and 5.7% by Medicaid. More than 40 providers were involved in the care of at least one PrEP pt, with the largest PrEP census by provider being 52. In EMR review, 36 PrEP pts had been in a prior PrEP study; 61 had a bacterial STD diagnosed within 60 days of initiating PrEP, and 113 had used post-exposure prophylaxis (PEP) previously. Thus far, only one pt prescribed PrEP became HIV-infected; this occurred very soon after initiating PrEP.

Conclusions: PrEP uptake has increased among MSM pts in a Boston community health center over the past 3 years, with the greatest increase in recent months. The racial/ethnic diversity of PrEP users has increased, with a large proportion of PrEP pts being < 30 y.o. Although some patients continued using PrEP after being in a research study, more PrEP pts were prescribed PrEP after a recent STD or after having used PEP, without prior PrEP experience. These findings suggest increased FH clinician and MSM pt acceptance of PrEP as part of a comprehensive HIV prevention package.

973 Barriers to Effective Prevention: Applying a PrEP Care Continuum to a US Cohort of Black and White MSM

Colleen F. Kelley; Erin M. Kahle; Aaron Siegler; Carlos del Rio; Travis Sanchez; Patrick Sullivan; Eli S. Rosenberg

Emory University, Atlanta, GA, US

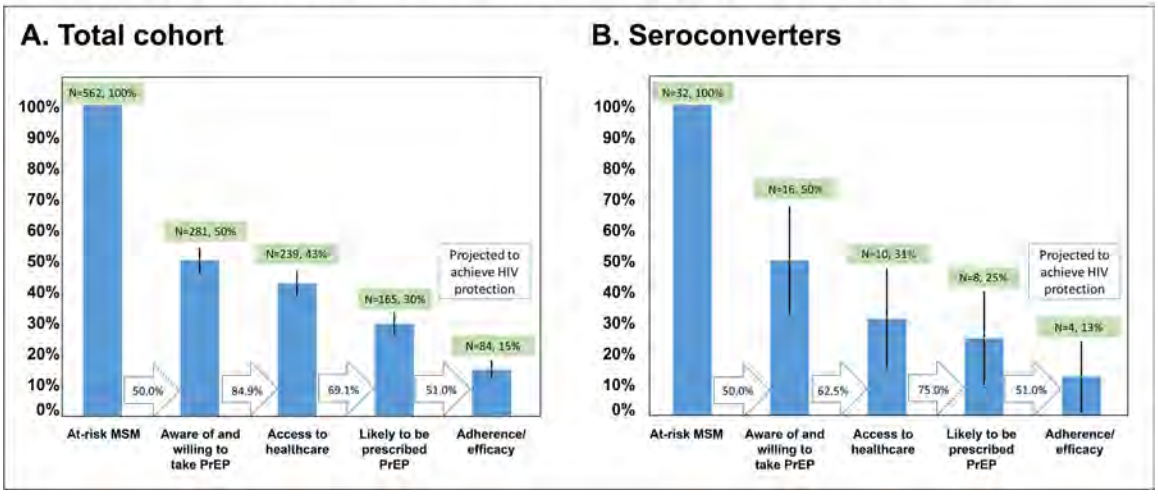
Background: Reductions in HIV incidence with pre-exposure prophylaxis (PrEP) for men who have sex with men (MSM) will require significant coverage of those at risk. We propose a simplified framework, similar to the HIV Care Continuum, to achieve protection from HIV with PrEP as follows: 1. At-risk MSM; 2. Aware of and willing to take PrEP; 2. Access to healthcare; 3. Receiving a PrEP prescription; and 4. Adhering to PrEP. We evaluated the PrEP Care Continuum on a cohort of Southern MSM and projected how many MSM might achieve protection from HIV.

Methods: InvolveMENt was an HIV incidence cohort of 562 black and white sexually active, non-monogamous, HIV-negative MSM in Atlanta, Georgia conducted from 2010-2014 with 32 observed HIV seroconversions, and which was used to apply the PrEP Care Continuum under optimistic estimates. Step 1 included all MSM in this at-risk cohort. Step 2 used awareness/willingness estimates. Step 3 used the percent of cohort men with health insurance or ACA eligibility in GA. Step 4 used the percent of cohort men meeting CDC PrEP eligibility guidelines. Step 5 applied the 51% adherence/efficacy estimate from the iPrex OLE study. Proportions with 95% confidence intervals (CI) of MSM in the total cohort and seroconverters projected to reach each step were calculated. We performed sensitivity analyses for a 20% increase at each continuum step individually and for all steps.

Results: Awareness/willingness was estimated at 50% for both analyses. Sixty-five percent of MSM in the total cohort, and 43% of seroconverters had health insurance; an additional 20% were ACA eligible in both groups. Sixty-nine percent of MSM in the total cohort and 75% of seroconverters met PrEP eligibility guidelines. The PrEP Care Continuum **(figure)** resulted in 15% (84/562; CI 12, 18%) of the cohort and 13% (4/32; CI 1, 23%) of seroconverters achieving theoretical protection from HIV. Increases in each step individually by 20% yielded a maximum protection of 21% for the cohort and 16% for seroconverters, while increasing all steps by 20% yielded 44% and 38% protection respectively.

Figure

Estimated PrEP Care Continuum for a US Cohort of Black and White MSM



Conclusions: Even with generous, 'best-case scenario' estimates, few Atlanta MSM will achieve protection from HIV with PrEP given the significant barriers described in the PrEP Care Continuum. Each step of the proposed continuum represents a critical intervention point. Novel strategies for PrEP delivery are needed to achieve the necessary effectiveness for MSM at risk of HIV.

974 Provider Prescription of Preexposure Prophylaxis (PrEP) for HIV Infection

Shikha Garg; John Weiser; Linda Beer; Jacek Skarbinski

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: PrEP with daily oral fixed-dose combination tenofovir/emtricitabine is safe and effective in reducing the risk of HIV acquisition. While official PrEP guidelines were only released in 2014, interim guidance for use of PrEP in certain high-risk groups has been available since 2011. Data on provider uptake of interim PrEP guidance are lacking.

Methods: U.S. care providers were surveyed during June 2013–January 2014 to estimate the weighted prevalence of ever prescribing PrEP and to describe patients for whom PrEP was prescribed. Physicians, nurse practitioners, or physician assistants who had completed training and who provided care to HIV-infected patients were eligible for the survey. We used prevalence ratios (aPR) estimated from multivariable logistic regression to investigate the association between provider characteristics, including demographic factors and HIV care experience, and PrEP prescription. Analyses accounted for clustering, unequal selection probabilities, and non-response.

Results: Surveys were completed by 1234 of 2023 eligible providers (adjusted response rate 64%). Among HIV care providers who responded to questions about PrEP prescription and who also reported providing care to HIV-infected and non-HIV-infected patients (n=935), 26% (95% confidence interval: 20–31) ever prescribed PrEP. Among providers prescribing PrEP, 74% prescribed to men who have sex with men, 23% to men who have sex with women, 30% to women who have sex with men, 23% to uninfected partners in serodiscordant couples trying to conceive, and 1% to injection drug users. Providing direct and continuous care to greater than 50 HIV-infected patients, male gender and gay/lesbian/bisexual orientation were all provider characteristics independently associated with PrEP prescription (Table).

Table. U.S. HIV Care Provider Characteristics Independently Associated With Prescription of Pre-exposure Prophylaxis for HIV Infection

Characteristic	Weighted Prevalence (95% CI)	Rao Scott P value	Unadjusted Prevalence Ratio (95% CI)	Adjusted Prevalence Ratio (95% CI)
Age in years				
<40	19 (12-27)	0.4222	Ref	—
40-59	26 (18-34)		1.3 (0.8—2.2)	
≥60	29 (18-40)		1.5 (0.8—2.7)	
Gender				
Male	32 (24-39)	0.0003	2.0 (1.4—2.9)	1.5 (1.0—2.2)
Female	16 (11-21)		Ref	Ref
Race				
White, non-Hispanic	26 (20-31)	0.7288	Ref	—
Black, non-Hispanic	35 (9-62)		1.4 (0.6—3.9)	
Hispanic	23 (10-36)		0.9 (0.5—1.7)	
Sexual Orientation				
Heterosexual	21 (16-27)	0.0082	Ref	Ref
Gay/lesbian/bisexual	50 (34-66)		2.4 (1.5—3.6)	2.0 (1.4—3.1)
Profession				
Physician	25 (20-30)	0.5784	Ref	—
NP or PA	29 (14-44)		1.1 (0.7—2.0)	
Years caring for HIV patients				
0-10	25 (15-35)	0.7898	Ref	—
11-20	25 (17-32)		1.0 (0.6—1.6)	
>20	28 (21-36)		2.0 (0.7—1.9)	
Number HIV patients provide direct/continuous care to				
0-50	14 (7-22)	0.0029	Ref	Ref
51-200	29 (20-39)		2.0 (1.2—3.5)	2.2 (1.1—4.1)
>200	39 (28-50)		2.7 (1.4—5.2)	2.4 (1.1—5.3)
>50% patients MSM				
Yes	31 (24-37)	0.0582	1.5 (1.0—2.2)	—
No	21 (13-29)			

PrEP = pre-exposure prophylaxis; CI = confidence interval; NP = nurse practitioner; PA = physician assistant; MSM = men who have sex with men

Conclusions: PrEP is a powerful HIV prevention tool, yet at baseline, only one-fourth of U.S. providers who care for both HIV-infected and non-HIV-infected patients reported ever prescribing PrEP based on interim guidance. Although provider uptake may increase with the release of formal PrEP guidance in 2014, targeted efforts should be made to increase PrEP prescription by providers who care for few or no HIV-infected patients and who may have limited experience prescribing antiretroviral therapy.

TUESDAY, FEBRUARY 24, 2015

Session P-V4 Poster Session — Poster Hall

2:30 pm – 4:00 pm

PrEP: Measures and Correlates of Adherence

975 Urine Assay for Tenofovir to Monitor Adherence to Tenofovir-Emtricitabine as PrEP

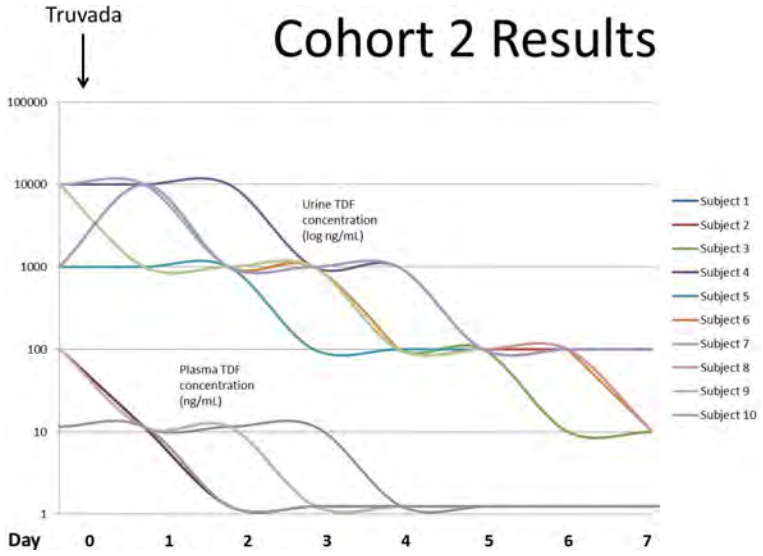
Helen C. Koenig[1]; Karam Mounzer[1]; **Giffin W. Daughtridge**[1]; Caroline E. Sloan[1]; Linden Lalley-Chareczko[2]; Ganesh Moorthy[3]; S. Caitlin Conyngham[2]; Elizabeth Ketner[1]; Luis J. Montaner[4]; Pablo Tebas[1]

[1]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, US; [2]Philadelphia FIGHT, Philadelphia, PA, US; [3]The Children's Hospital of Philadelphia, Philadelphia, PA, US; [4]Wistar Institute, Philadelphia, PA, US

Background: Tenofovir-Emtricitabine (TDF/FTC) is approved for pre-exposure prophylaxis (PrEP) for HIV infection. Adherence is critical for the success of PrEP, but current adherence measurements (self-report) and plasma tenofovir (TFV) levels are inadequate tools for real time adherence monitoring. Our goal was to develop and validate a urine assay for the measurement of TFV levels to objectively monitor adherence to PrEP.

Methods: We developed a semi-quantitative urine assay using liquid chromatography mass spectrometry with high sensitivity/specificity for TFV. This assay allowed us to determine TFV concentrations in log categories between <10 ng/ml to > 10,000 ng/ml. To clinically validate the assay we conducted 3 cohort studies: 1) A cross sectional study of 10 HIV positive subjects with undetectable HIV viral loads on a TFV-based regimen to evaluate the qualitative relationship of urine TFV levels to plasma levels, 2) A single dose study of TDF/FTC in 10 healthy subjects to evaluate TFV clearance in plasma and urine over 7 days, 3) A 16 week study of 10 HIV negative subjects receiving daily PrEP to evaluate concordance between plasma and urine over time.

Results: Cohort 1 demonstrated 100% concordance between presence of TFV in plasma and urine (PPV 100%, 95% CI, 0.63-1.0; NPV 100%, 95%CI, 0.05-1.0). TFV concentration was 3-4 logs higher in urine than plasma. In cohort 2, TFV was detected for >7 days in urine and 2-4 days in plasma after a single dose of TDF/FTC. Urine TFV was cleared in a log-linear fashion, with a direct correlation of urine levels to time since last dose. The urine assay was 2 logs more sensitive than serum over 7 days. In cohort 3, TFV was detected in 93% of urine samples (concentration range: >10 to >10,000 ng/mL) and 74% of plasma samples (concentration range: >10 ng/ml to >100 ng/ml). Urine TFV concentration > 1000 ng/ml was highly predictive of presence of TFV in plasma (>10 ng/ml) (PPV 0.88, 95%CI, 0.69-0.97; NPV 0.88, 95%CI, 0.47-0.99), suggesting that the urine assay could be used to distinguish between recent adherence as defined by a dose of TFV within 48 hours (>1000 ng/ml), low adherence (>10 to >100 ng/ml), and non-adherence as defined by last dose more than one week prior (<10 ng/ml).



Conclusions: We provide proof-of-concept that a semi-quantitative urine assay measuring levels of TFV could be further developed into a point of care test to monitor adherence to PrEP.

976 Comparison of Adherence Measures in a Clinical Trial of Preexposure Prophylaxis

Davis C. Muganzi[1]; Jessica Haberer[2]; Yap Boum[1]; Nicholas Musinguzi[1]; Allan Ronald[4]; Connie Celum[3]; Jared Baeten[3]; David R. Bangsberg[4]

[1]Mbarara University of Science and Technology, Kampala, Uganda; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]University of Washington, Seattle, WA, US; [4]University of Manitoba, Winnipeg, Canada

Background: No gold standard exists for adherence measurement. Self-report is commonly used but it is subjective. Objective measures are more costly and difficult to implement. Research is limited on the performance of these measures for pre-exposure prophylaxis (PrEP) against HIV infection.

Methods: The Partners PrEP Ancillary Adherence Study collected the following adherence measures in 1,147 HIV-uninfected partners in serodiscordant couples from 3 Ugandan sites in the Partners PrEP Study (a randomized placebo-controlled trial of tenofovir-based PrEP collected).:

Monthly self-report

Rating- "How well have you taken your study tablets?"

Frequency- "How often do you take your study tablets?"

Percent- "What percent of the time were you able to take your study tablets?"

Objective measures

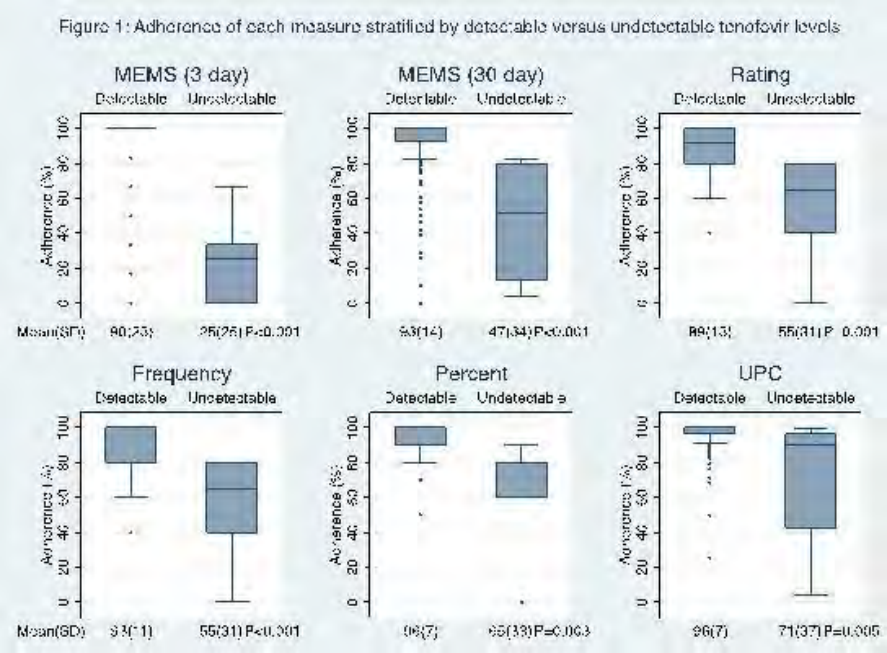
Electronic monitoring (MEMS, downloaded monthly)

Unannounced pill counts (UPC, performed monthly at home)

Plasma tenofovir level (month 6 in a randomly selected subset of 228 participants on active drug)

Rating and frequency responses were recorded on a 6-point Likert scale and converted to percents (e.g., most of the time=80%). Monthly adherence over 6 months was compared by Spearman correlation and to tenofovir level (detectable ≥0.32ng/ml) by regression analysis with the Huber White sandwich variance estimator.

Results: A total of 1,143 individuals were included in the analysis; median age 34 (IQR: 30-40), 606 (53%) were male. Median (IQR) adherence by each measure was as follows: rating 90% (83-93), frequency 93% (90-97), percent 97% (93-98), MEMS 97% (91-99), and UPC 98% (96-99). Correlations among self-report measures ranged from 0.61-0.67 ($p<0.001$). Correlations of self-report measures ranged from 0.31-0.36 with UPC ($p<0.001$) and 0.23-0.25 with MEMS ($p<0.001$). Comparisons of adherence levels with detection of tenofovir are shown in Figure 1.



Conclusions: All measures revealed high adherence. The distribution of adherence varied among types of self-report queries; the widest was seen with rating, suggesting greater potential utility for identifying individuals with adherence challenges. Correlation with MEMS and UPC was significant, but modest, likely reflecting differences in measurement techniques (e.g., daily variation vs monthly summaries). All measures significantly discriminated between detectable and undetectable tenofovir levels; however, MEMS performed best and is less resource intensive than UPC.

977 Self-Reported Recent PrEP Use Has Strong Relation to Drug Detection in iPrEx OLE

Rivet Amico[1]; Vanessa McMahan[2]; Megha Mehrotra[2]; Peter L. Anderson[2]; Juan Guanira[2]; Valdilea Veloso[2]; Robert M. Grant[2]
the iPrEx study team

[1]University of Michigan, Ann Arbor, MI, US; [2]Gladstone Institute, San Fransicso, CA, US

Background: Gross inaccuracies in participant-reported adherence has dampened or eliminated confidence in self-report as a method to characterize PrEP use. Sophisticated measurement strategies available in clinical trials, however, are unlikely candidates for adoption in clinical practice, contributing to concerns about PrEP roll-out. Self-report of self-selected open-label PrEP use has not been characterized to date and may differ from observations in efficacy trials. We examined the performance of self-report in this specific context using self-reported recent PrEP use among iPrEx open label extension (OLE) participants contrasted to drug detection.

Methods: All iPrEx OLE participants choosing to receive PrEP at the 11 geographically-diverse research sites were informed that a blood specimen collected at some point during their first 12 weeks of receiving PrEP would be evaluated for drug levels and results would be shared with them. Recall of dates of last 3-doses taken was collected via interview at all on-drug visits. Drug levels were determined using blood plasma by liquid chromatography tandom MS having a lower limit of quantification of 10 ng/ml, reflecting dosing in the past 3 days. Self-report (at least one dose in the past 3-days vs no dosing) was compared to drug detection (detected versus not detected) using binary logistic regression.

Results: 1172 participants had drug levels matched to self-report. The vast majority reported having had at least one dose in the past three days (84%) and of these 83% had detectable drug (PPV). Among the 16% reporting not having dosed, 82% had no drug detected (NPV). Sensitivity of self-report was 96%; specificity was 48%. Self-report was highly associated with drug level, OR 21.57 [14.42-32.26], which retained significance when controlling for site or whether the report was of taking or not taking PrEP. Age interacted with self-report and drug detection; among those reporting recent dosing, age positively associated with having drug detected.

Conclusions: In this study where participants had the choice of receiving open label PrEP, reports of recent PrEP use had high association and moderate concordance with drug detection. Participants misclassified as "adherent' via self-report tended to be younger, suggesting the need to develop alternative assessment strategies for younger PrEP users. In contrast to data from PrEP efficacy trials, results suggest that use of self-report in practice may be a valuable tool.

978LB HPTN 067/ADAPT Cape Town: A Comparison of Daily and Nondaily PrEP Dosing in African Women

Linda-Gail Bekker[1]; james Hughes[2]; Rivet Amico[4]; Surita Roux[3]; Craig Hendrix[5]; Peter L. Anderson[6]; Bonnie Dye[7]; Vanessa Elharrar[8]; Michael J. Stirratt[9]; Robert Grant[10]

[1]Dept of Medicine and Institute of Infectious Disease and Molecular Medicine, Cape Town, South Africa; [2]HIV Prevention Trials Network, Seattle, WA, US; [3]The Desmond Tutu HIV Centre, Cape Town, South Africa; [4]University of Michigan, Ann Arbor, MI, US; [5]Johns Hopkins University, Baltimore, MD, US; [6]University of Colorado, Aurora, CO, US; [7]FHI360, Durham, NC, US; [8]PSP/DAIDS/NIAID/NIH, Bethesda, MD, US; [9]Center for Mental Health Research on AIDS, Bethesda, MD, US; [10]University of California, San Francisco, CA, US

Background: HIV pre-exposure chemoprophylaxis (PrEP) is becoming a standard of prevention care in many countries; however concerns about costs and side effects can limit uptake. The HPTN 067 ADAPT trial, a Phase II, randomized, open-label clinical trial of oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) PrEP, included a cohort of South African women in Cape Town. The study investigated whether a nondaily versus daily regimen of FTC/TDF, resulted in equivalent prophylactic coverage of sex events, less tablets required and fewer side effects.

Methods: After 6 weeks of directly observed dosing (DOT), participants were randomly assigned to one of three unblinded PrEP dosing regimens for 24 weeks of self-administered dosing: daily (D), twice weekly with a post-intercourse boost (T), or before and after intercourse (E). Pills were dispensed from a Wisepill device that recorded each opening. Participants were contacted weekly to review Wisepill data and sex events. Plasma and PBMC were collected and analyzed for tenofovir (TFV) and FTC and their active metabolites at 10 and 30 weeks. Coverage was defined as ≥1 pill taken in the 4 days before and ≥1 pill taken in the 24 hours after sexual intercourse. Adherence was defined as the percentage of recommended pills taken for each regimen.

Results: Of 191 women enrolled in the DOT phase, 179 were randomized to the self-administered phase. Median age was 26 years (range 18-52), 80% were unmarried and 83% unemployed. PrEP coverage differed by arm as shown in the table (P<0.001). Fewer pills were required in T and E compared with D (p < 0.001). Side effects were uncommon in D, and less frequent in T and E. Adherence to the assigned regimen was greater in D compared with T and E (P<0.001); adherence to post-intercourse dosing in the nondaily arms was low. When sex was reported in the prior week, both plasma TFV (consistent with ≥1 pill in prior week) and PBMC TFV diphosphate (consistent with ≥2 pills in prior week) were detected in more women in D at weeks 10 and 30, compared with T and E (p < 0.05). HIV seroconversions were not significantly different by arm.

Randomization at 6 wks	Daily (D)	Time-Driven (T)	Event-driven (E)	p-value[1]
N	60	59	60	
Median age	25	26	25	
HIV seroconversions	1	2	2	0.87
Total sex events over full study	1954	1078	1533	0.002
% total events fully covered	75	56	52	<0.001
% total events partly covered (pre only, post only)	22 (21, 1)	39 (30, 9)	41 (33, 8)	
% total events not covered	3	6	7	
Total required pills	9758	3629	2205	<0.001
Total % adherence	76	65	53	<0.001
% detectable in plasma when reporting sex in last 7 days (at 10 wks follow-up; at 30 wks of follow-up)	92.5; 79.3	86.4; 62.5	80.0; 53.1	0.03
% ≥9.1 fmol/10^6 cells in PBMC when reporting sex in last 7 days (at 10 wks follow-up; at 30 wks of follow up)	80.0; 65.5	50.0; 45.8	57.1; 32.3	0.006

[1]*p-value comparing three arms*

Conclusions: The majority of women took oral PrEP when made available in an open label study. Daily dosing resulted in better coverage of sex acts and adherence, and higher drug levels. Daily dosing may foster better habit formation and provide the most forgiveness for missed doses at observed adherence levels. These findings support current recommendations for daily use of oral FTC/TDF PrEP in women.

979 Correlates of Early Adherence in VOICE PrEP Trial Differ Between Oral and Vaginal Products

Ariane van der Straten[1]; Elizabeth R. Brown[2]; James Dai[2]; Craig Hendrix[3]; Karen Liu[2]; Cynthia Grossman[4]; Z M. Chirenje[5]; Jeanne Marrazzo[6]

[1]RTI, San Francisco, CA, US; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]National Institute of Mental Health (NIMH), Bethesda, MD, US; [5]University of Zimbabwe–University of California San Francisco Research Collaboration, Harare, Zimbabwe; [6]University of Washington, Seattle, WA, US

Background: VOICE was a phase IIB trial of daily oral tenofovir disoproxil fumarate (TDF), oral TDF-emtricitabine (FTC), and 1% vaginal tenofovir (TFV) gel for HIV chemoprevention, in Uganda, Zimbabwe and South Africa (RSA). Plasma TFV levels objectively measure product use and correlate with efficacy. We measured plasma TFV levels (≥0.3 ng/mL) in a subset of VOICE participants on active products at their first quarterly visit, and assessed factors associated with early product use.

Methods: Of 5029 enrollees, we analyzed available TFV levels in plasma samples taken at 3 months post-randomization from women assigned to active product and not on product hold. We examined a pre-determined set of demographic, socio-behavioral and clinical factors assessed at baseline or 3 months and their association (at p<0.05 significance level) with TFV detection in the oral and gel groups. All analyses were weighted to adjust for the sampling design. Weighted generalized linear models with a log-link and robust standard errors were fitted to estimate prevalence ratio (PR) of detectable TFV in plasma, adjusting for country.

Results: Of 1146 participants assessed at 3-month follow-up, 33% had TFV detectable in the oral group (N=637) and 27% in the gel group (N=509), respectively. TFV detection by group and country is summarized in the table below. Controlling for country, factors associated with TFV detection in the oral group were: receiving material support from partner (PR=0.64; p=0.02) and frequent alcohol use (PR=1.93; p<0.01). In the gel group, factors associated with TFV detection were: age ≥25 (PR=1.6; p=0.03), partner disapproval of product use (PR=0.34, p=0.02) and social harm (PR=0.23 p=0.04). In both groups, moderate perceived HIV risk was associated with detecting TFV.

		Oral group-TFV detection			Gel group-TFV detection		
		prevalence	PR	p val	prevalence	PR	p val
Country	Uganda	50%	1.58	<0.001	13%	0.51	ns
	Zimbabwe	44%	1.39	0.01	39%	1.49	0.04
	RSA	31%	ref		26%	ref	

Conclusions: In these VOICE participants, use of oral tablets and gel at initial PK assessment varied by country. Further, different factors correlated with product use in the oral and gel groups, suggesting geographical, demographic and relationship difference in end-users characteristics for different routes of administration. This study adds to the growing body of evidence that choice of biomedical prevention options will be critical to address the varying prevention needs of women at risk of HIV.

980 Intimate Partner Violence Is Associated With Low PrEP Adherence in African Women

Sarah T. Roberts[1]; Connie Celum[1]; Nelly Mugo[3]; Jessica Haberer[2]; Craig R. Cohen[4]; Elizabeth Irungu[5]; James N. Kiarie[6]; Edwin Were[7]; Jared Baeten[1]
On behalf of the Partners PrEP Study Team

[1]University of Washington, Seattle, WA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Kenya Medical Research Institute, Nairobi, Kenya; [4]University of California San Francisco, San Francisco, CA, US; [5]Kenyatta National Hospital, Nairobi, Kenya; [6]University of Nairobi, Nairobi, Kenya; [7]Moi University, Eldoret, Kenya

Background: Intimate partner violence (IPV) has been associated with increased risk for HIV acquisition. Women who experience IPV are thus a potential target population for pre-exposure prophylaxis (PrEP) to prevent HIV infection. However, high adherence levels are required for PrEP efficacy, and IPV exposure is associated with lower adherence to other medication regimens. Studies have not evaluated whether IPV is associated with low PrEP adherence.

Methods: We evaluated the association between IPV exposure and PrEP adherence among HIV-uninfected women enrolled in the Partners PrEP Study, a randomized, placebo-controlled trial of oral, daily PrEP in African HIV serodiscordant couples. Exposure to IPV was assessed at monthly study visits by asking whether the participant had been verbally, physically, or economically abused by her partner since the last visit, or in the last 3 months at enrollment. At each visit, women were categorized as "recently IPV-exposed" (IPV reported in the last 3 months), "previously IPV-exposed" (IPV reported more than 3 months ago) or "IPV-unexposed" (no report of IPV to date). Adherence to PrEP was measured monthly by clinic-based pill count and was dichotomized *a priori* as low (<80%) or high (≥80%). Adherence was measured for each scheduled study visit at which the participant was eligible to receive PrEP. Missed visits were assigned 0% adherence.

Results: Among 1,785 HIV-uninfected women, 288 (16.1%) reported IPV at 437 study visits over 12-48 months of follow-up. Reported IPV included verbal abuse at 371 visits (84.9%), physical abuse at 228 visits (52.2%), and economic abuse at 163 visits (37.3%). Mean PrEP adherence was 95.3% (SD 19.9%). Women had low adherence at 88 (8.0%) of 1100 recently IPV-exposed visits and 433 (7.9%) of 5,471 previously IPV-exposed visits, compared to 2,962 (6.8%) of 43,562 IPV-unexposed visits. After adjusting for age, years of education, study site, any additional sex partners, and time on study, recently IPV-exposed women had a 52% higher likelihood of low PrEP adherence (adjusted OR 1.52, 95% CI 1.16-1.99, p=0.002). Previous IPV exposure was not associated with adherence (p=0.77).

Conclusions: Among HIV-uninfected women in the Partners PrEP Study, adherence to PrEP was very high overall. Women who reported IPV in the past 3 months were at increased risk of low PrEP adherence. If PrEP is targeted towards women exposed to IPV, the risk of low adherence should be recognized and strategies to promote high PrEP adherence should be evaluated.

WEDNESDAY, FEBRUARY 25, 2015

Session P-V5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

PrEP: Evaluating Potential Harm

981 Reversibility of Kidney Function Decline in HIV-1–Uninfected Men and Women Using Preexposure Prophylaxis

Kenneth K. Mugwanya[1]; Christina Wyatt[2]; Connie Celum[1]; Deborah Donnell[3]; Nelly Mugo[4]; James N. Kiarie[5]; Allan Ronald[6]; Jared Baeten[1]
On behalf of the Partners PrEP Study Team

[1]University of Washington, Seattle, WA, US; [2]Mount Sinai School of Medicine, New York, NY, US; [3]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [4]Kenya Medical Research Institute, Nairobi, Kenya; [5]University of Nairobi, Nairobi, Kenya; [6]University of Manitoba, Winnipeg, Canada

Background: Tenofovir disoproxil fumarate pre-exposure prophylaxis (PrEP) use is associated with a small but statistically significant decline in estimated glomerular filtration rate (eGFR). We investigated the occurrence and reversibility of eGFR decline among HIV-1 uninfected adults discontinuing PrEP.

Methods: Data are from the Partners PrEP Study, a trial of daily oral tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC)/TDF PrEP among 4747 African HIV-1 uninfected men and women who had normal baseline renal parameters. Renal function was assessed at baseline, month 1, and then quarterly while on study medication and up to 2 monthly visits in the post-study drug follow-up phase. eGFR was calculated using the Chronic Kidney Disease Epidemiolgy Collaboration Equation.

Results: A total of 3944 individuals had a post-study drug visit within 12 weeks of drug discontinuation (1277 in TDF group, 1309 in FTC-TDF group, and 1358 for placebo); 64% were male, median age was 34 (range 18–64) years, and mean eGFR was similar at baseline (p>0.05). Median time on study drug was 33 (IQR 25–36) months. Compared to placebo (Figure 1), mean eGFR for PrEP was slightly but statistically significantly lower at the last on-treatment visit (128 mL/min/173m^2 for TDF and FTC-TDF vs 130 mL/min/173m^2 for placebo; p≤0.01). This difference reversed to within baseline levels by 4 weeks after PrEP discontinuation (130 mL/min/173m^2 for TDF, 129 mL/min/173m^2 for FTC-TDF vs 130 mL/min/173m^2 for placebo eGFR; p>0.2 for all). Consistent patterns were observed for serum phosphorus.

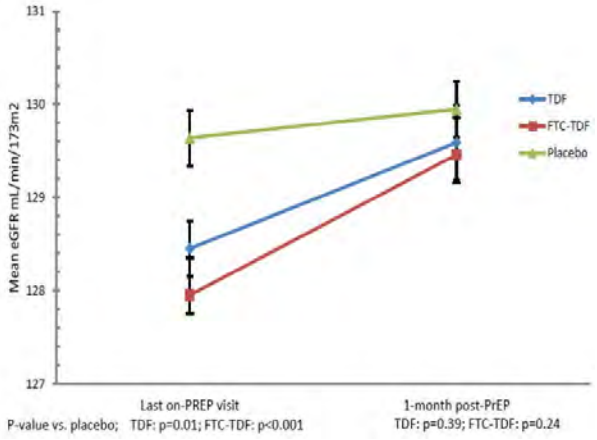


Figure 1. Change in mean eGFR after discontinuation of TDF-based PrEP

Conclusions: In this large study among African men and women who had a median TDF-exposure of 33 months, the reduction in mean eGFR was small and returned to within baseline levels by 4 weeks after discontinuation of TDF-based PrEP.

982 Minor Drug-Resistant Variants Infrequently Detected in Seroconverters From MTN 003 (VOICE)

Constantinos Panousis[1]; Elias K. Halvas[1]; Cliff Kelly[2]; Jeanne Marrazzo[3]; Z M. Chirenje[4]; John W. Mellors[1]; **Urvi M. Parikh**[1]
On behalf of the MTN 003 Protocol Team
[1]University of Pittsburgh, Pittsburgh, PA, US; [2]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [3]University of Washington, Seattle, WA, US; [4]UZ-UCSF Collaborative Research Programme, Harare, Zimbabwe

Background: Minor (low frequency) drug-resistant variants selected by antiretroviral (ARV)-based prevention could negatively impact response to future antiretroviral therapy. We previously reported (Marrazzo et al., NEJM 2014) that acquired resistance to ARV-based products in the MTN 003 (VOICE) study was rarely detected by standard population based genotype analysis (1/212 participants receiving active product), with no cases of tenofovir (TFV) resistance and only one case of emtricitabine (FTC) resistance with M184V, but minor resistant variants were not excluded. Here, we assess the frequency of minor resistant variants among seroconverters in the VOICE study.

Methods: VOICE was a safety and effectiveness study of TFV-based products for HIV prevention conducted at 15 sites in South Africa, Zimbabwe and Uganda. Participants were randomized to vaginal TFV 1% gel, oral tenofovir disoproxil fumarate (TDF), oral FTC/TDF, or oral or gel placebo. Plasma for resistance testing was collected from seroconverters on study when HIV infection was confirmed by rapid testing and Western blot. Plasma samples from 301 seroconverters with standard genotype results were analyzed by allele-specific PCR (ASPCR) to quantify % mutant frequency down to 0.1% for K65R, M184V and M184I, and 0.3% for K70E. Mutant frequency was analyzed by treatment arm and whether TFV was detectable in plasma (>0 ng/mL).

Results: Of 301 women without TFV resistance by population genotyping, 3/276 had K65R (0.5-15% mutant frequency) and 0/283 had K70E detected by ASPCR. Of 300 women without FTC resistance by population genotyping, 1/288 had M184V (0.5% mutant frequency) and 11/285 had M184I (0.5-5.2% mutant frequency) detected by ASPCR. 1 participant with M184V detected by standard genotyping had resistance confirmed by ASPCR (98% mutant frequency). The detection of low frequency mutants did not differ across treatment arms or with the detection of tenofovir at any follow-up visit.

Conclusions: Fifteen of 289 (5%) participants in the VOICE trial had low frequency FTC or TFV resistance detected by ASPCR but mutant detection was not associated with treatment arm or detectable TFV suggesting transmitted resistance or spontaneously arising mutants of unknown clinical significance. Low product use in the VOICE trial could explain the infrequent selection of resistance among seroconverters.

983 PrEP-Selected Drug Resistance Fades by Six Months Following Drug Cessation

Julie F. Weis[1]; Jared Baeten[2]; Ruth Kanthula[3]; Connor McCoy[1]; Lisa Frenkel[2]; Nelly Mugo[2]; Frederick Matsen[1]; Julie M. Overbaugh[1]; Connie Celum[2]; Dara A. Lehman[1]
[1]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [2]University of Washington, Seattle, WA, US; [3]Seattle Children's Research Institute, Seattle, WA, US; [4]Fred Hutchinson Cancer Research Center, Seattle, WA, US

Background: Pre-exposure prophylaxis (PrEP) significantly reduces HIV-1 transmission. However, selection for drug resistance may occur when PrEP is initiated during unrecognized acute infection or in breakthrough infections during periods of low PrEP adherence. In these cases it remains unclear how long resistance persists after discontinuation of PrEP.

Methods: The Partners PrEP Study was a randomized trial of PrEP as emtricitabine coformulated with tenofovir disproxil fumarate (FTC/TDF), or TDF alone compared to placebo. FTC is known to select for the resistance mutation M184V and TDF for K65R and K70E. We previously reported that PrEP-related mutations were detected by 454 ultra-deep sequencing in 9 of 121 HIV seroconverters tested at detection of seroconversion when study drug was stopped and/or one month later. In this current study, we used 454 sequencing to detect and quantify PrEP-related mutations at 6, 12, and 24 months after PrEP cessation in plasma samples from these 9 individuals. A sample was classified as resistant when the frequency of mutant sequences was significantly higher than what was observed in matched controls using Fisher's exact test, correcting for a 5% false-discovery rate.

Results: All PrEP-selected mutations were no longer present by 6 months and remained undetectable at 12 and 24 months after seroconversion. This included 1 individual with both TDF-selected mutations K65R and K70E present when seroconversion was detected (56% and 10% respective frequency), and 4 individuals with M184V (ranging from 1% to 99% at detection of seroconversion). Three seroconverters (2 placebo, 1 TDF) had evidence of M184I at seroconversion, which is naturally polymorphic and was not due to PrEP selection. In these 3 cases, M184I fluctuated at low levels, from undetectable up to 6% throughout follow-up. One individual was lost to follow-up.

Conclusions: Using highly sensitive assays, PrEP-selected resistance in plasma decreases to below detection by six months following drug cessation and remains undetectable for at least 24 months. Even high levels of resistance mutations during acute infection decrease rapidly in the absence of ongoing PrEP exposure.

984 Randomized Controlled Trial on ART Outcomes in Tenofovir Gel Trial Seroconvertors

Anushka Naidoo; Nivashnee Naicker; Lise Werner; Nigel Garrett; Sarah Dlamini; Villeshni Asari; Nelisile Majola; Cheryl Baxter; Quarraisha Abdool Karim; Salim S. Abdool Karim
Center for the AIDS Program of Research in South Africa, Durban, South Africa

Background: Prior to promoting tenofovir gel for HIV prevention in women, it is important to know whether tenofovir gel users who acquire HIV infection can be treated with tenofovir containing antiretroviral treatment (ART) with good clinical outcomes. The CAPRISA009 randomised clinical trial assessed ART outcomes in women who acquired HIV during tenofovir gel trials.

Methods: Seroconvertors from the CAPRISA004 tenofovir gel effectiveness trial and CAPRISA008 tenofovir gel implementation trial were recruited into the CAPRISA009 study when eligible for ART initiation (CD4 count <350 cells/μl, pregnancy or AIDS-defining illness). Women were randomised to a tenofovir-containing or tenofovir-sparing (zidovudine-containing) regimen. CD4 counts and viral loads (VL) were monitored at baseline and follow-up visits. Clinical outcomes, virological suppression (VL <50 copies/ml), CD4 counts, adverse events and drug switches were compared between the two groups using Fisher's exact and Wilcoxon rank sum tests.

Results: From June 2011 to August 2014, 59 women were enrolled and followed-up for a median of 13 months (IQR 6-19). Twenty-nine women (7 tenofovir gel exposed) were randomized to a tenofovir-containing and 30 (9 tenofovir gel exposed) to a tenofovir-sparing regimen. Median baseline CD4 count and VL were 361 cells/μl (IQR 275–420) and 4.64 log copies/ml (IQR 4.01-5.11), and did not differ by ART assignment. Overall VL suppression rates were 85.7% and 76.2% at 6 months (p=0.70) and 84.2% and 76.5% at 12 months (p=0.68) in the tenofovir-containing and tenofovir-sparing groups. In women with prior tenofovir exposure, VL suppression rates were 100% and 50% at 6 months (p=0.14) and 100% and 25% at 12 months (p=0.17) in the tenofovir-containing versus tenofovir-sparing groups. Overall, median CD4 counts at 12 months were 577 cells/μl and 541 cells/μl (p=0.45) and 388 cells/μl and 549 cells/μl (p= 0.35) in tenofovir gel exposed women in the tenofovir-containing and tenofovir-sparing groups. Women randomised to a tenofovir-sparing regimen experienced a higher frequency of grade 3 or 4 AEs (33.3% vs 10.3%, p=0.06) and had more toxicity-related drug switches (26.7% vs. 0.0%, p< 0.01) compared to women receiving a tenofovir-containing regimen. There were no drug switches in women with prior tenofovir gel exposure.

Conclusions: Tenofovir-containing ART was effective and safer in tenofovir gel trial seroconvertors and should be recommended as the preferred treatment option for women with prior exposure to tenofovir gel.

985 Frequent Dapivirine Cross-Resistance of HIV from 1st-line ART Failures in S. Africa

Kerri J. Penrose[1]; Kristen A. Hamanishi[1]; Kelley C. Gordon[1]; Raquel V. Viana[2]; Carole L. Wallis[3]; John W. Mellors[1]; Urvi M. Parikh[1]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]Lancet Laboratories, Johannesburg, South Africa; [3]Lancet Laboratories/BARC-SA, Johannesburg, South Africa

Background: Two Phase III studies (IPM Ring Study and MTN ASPIRE) are currently evaluating whether monthly use of a vaginal ring containing dapivirine (DPV) prevents HIV infection in women. The rise of transmitted EFV- and NVP-resistant virus could reduce the protective efficacy of DPV. This study investigated DPV cross-resistance among recombinant subtype C viruses derived from individuals failing 1st-line NVP- or EFV-containing ART regimens in South Africa (SA).

Methods: Residual plasma samples, sent for routine HIV drug resistance testing, were collected from HIV-1 subtype C-infected individuals in SA failing EFV- or NVP-containing 1st-line ART after 6 months of treatment with HIV RNA >10000 c/mL and with ≥1 NNRTI drug resistance mutation (DRM) detected by population sequencing. Recombinant HIV-1_{LAI} containing bulk-cloned full-length RT sequences from 60 plasma samples had susceptibility determined for NVP, EFV and DPV in TZM-bl cells. Fold-change (FC) values were calculated using a composite IC_{50} from 13 HIV subtype C treatment-naïve samples from SA. Calculated *in vitro* IC_{90} values were compared to *in vivo* maximum plasma and vaginal fluid DPV concentrations with monthly ring use (C_{max}) and those achieved on day 28 of ring use (C_{28}) based on published data (Nel *et al.* AIDS 2014).

Results: 47/60 (78%) samples showed ≥10 fold resistance to DPV compared to treatment naïve samples and exhibited a median IC_{50} of 16 ng/mL (Table). 9/60 (15%) samples displayed 3 to 9 fold resistance with median IC_{50} of 1.0 ng/mL. Only 4/60 (7%) samples containing NNRTI DRM were susceptible to DPV. The median IC_{90} of all viruses with ≥3-fold DPV resistance (10,800pg/mL) exceeded observed plasma C_{max} during 1 month of ring use (355 pg/mL). By contrast, the DPV C_{28} in vaginal fluid (29 μg/mL) was 900X higher than median IC_{90} of viruses with ≥10-fold DPV resistance (0.031μg/mL). The most common DRM found in the ≥10 fold resistant category were K103N (27/47, 57%), V106M (14/47, 30%), and L100I (9/47,19%).

Resistance Category (FC)	# of samples (%) n=60	Median IC_{50} (range) ng/mL	Median FC
High (≥10)	47 (78%)	16 (1.4-71)*	106 (10-481)*
Intermediate (3-9)	9 (15%)	1.0 (0.4-1.4)	7 (3-9)
Susceptible (≤2)	4 (7%)	0.3 (0.2-0.4)	2 (2-2)

*Median excludes 16 samples above the max IC_{50} >132ng/mL and max FC >750-fold

Conclusions: 78% of HIV-1 from 1st-line treatment failures in SA exhibit ≥10-fold cross-resistance to DPV. This level of resistance exceeds expected plasma concentrations, but very high genital tract DPV concentrations from DPV ring use may be sufficient to block both wild type and resistant virus. Nevertheless, it is critically important to assess the frequency of transmitted and selected DPV resistance following DPV ring use.

986 Effect of TDF Monotherapy PrEP on Immune Function in Seroconverting Individuals

Marcel E. Curlin[1]; Michael T. Martin[1]; Punneeporn Wasinrapee[2]; Wanna Leelawiwat[2]; Boonyos Raengsakulrach[2]; Janet McNicholl[1]; Pravan Suntharasamai[3]; Udomsak Sangkum[3]; Suphak Vanichseni[3]; Kachit Choopanya[3]

[1]US Centers for Disease Control and Prevention (CDC), Apo, US; [2]Thailand Ministry of Public Health-Centers for Disease Control and Prevention Collaboration, Nothaburi, Thailand; [3]Bangkok Tenofovir Study Group, Bangkok, Thailand

Background: Tenofovir disoproxil fumarate (TDF) has been used in all major published clinical trials of HIV pre-exposure prophylaxis (PrEP), and is a component of the only drug (TDF/emtricitabine) currently approved for PrEP. However, little is known about the effect of TDF monotherapy on individuals seroconverting while receiving PrEP. We examined immune functions in Bangkok Tenofovir Study (BTS) participants randomized to placebo or TDF who seroconverted during the study.

Methods: All available post-infection blood specimens from all seroconverting participants were analyzed. We performed flow cytometry using standard antibody (Ab) panels to characterize differentiation and activation status of circulating CD4+ and CD8+ T cells, and intracellular cytokine staining (ICS) using overlapping HIV-1 peptides spanning Gag to characterize HIV-specific T lymphocyte responses. We measured HIV-1 NAb titers in blood against two tier-1 laboratory strains (SS1196.1 [subtype B] and Th023 [CRF01-AE]) using a luciferase reporter assay in TZM-bl cells. Treatment groups were compared using the Wilcoxon rank sum test.

Results: Forty-eight seroconverters (TDF = 14, placebo = 34) provided 128 specimens collected a median of 221 days (r 40-1159) post infection and 121 days (r 41-1159) after cessation of TDF use. In TDF recipients, CD8+ T cells had significantly lower expression of intermediate, transitional effector and central effector memory cell markers compared with placebo recipients ($p < 0.02$). TDF and placebo recipients did not differ in the distribution of CD4+ cells ($p > 0.05$). In TDF recipients, CD8+ and CD4+ T-cells had lower expression of activation markers (CCR5 +/- HLA-DR and CD38) and programmed cell death protein 1 ($p < 0.02$). There was no difference between groups in ICS responses, neutralizing Ab titers, plasma viral load (PVL), or CD4 count.

Conclusions: TDF PrEP was associated with a significant skewing of CD8+ differentiation from transitional and central memory states towards an effector phenotype, In addition, TDF recipients had reduced activation of CD4 and CD8 cells, and lower expression of one marker associated with programmed cell death on activated cells. However, we did not detect significant differences in functional cellular or humoral responses, absolute peripherally circulating CD8+ or CD4+ cell counts, or PVL between groups. These data indicate that TDF PrEP could have lasting effects on T cell differentiation and cellular exhaustion in individuals becoming HIV infected while on therapy.

987 The Impact of Preexposure Prophylaxis on Antibody Maturation in HIV-Infected Women

Oliver B. Laeyendecker[1]; Andrew D. Redd[1]; Martha Nason[3]; Andrew Longosz[1]; Quarraisha Abdool Karim[2]; Vivek Naranbhai[2]; Nigel Garrett[2]; Salim S. Abdool Karim[2]; Thomas C. Quinn[1]

[1]National Institute of Allergy and Infectious Diseases, Baltimore, MD, US; [2]CAPRISA, University of KwaZulu-Natal, Congella, South Africa; [3]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US

Background: The CAPRISA 004 pre-exposure prophylaxis (PrEP) randomized trial demonstrated that women who used a vaginal gel containing the antiretroviral drug Tenofovir (TFV) had a 39% lower chance of acquiring HIV. It is not known if topical TFV alters the antibody response to breakthrough HIV infection, although a previous study of TFV PrEP treated rhesus macaques demonstrated a delay in antibody avidity maturation but not in titer.

Methods: Using the BED capture enzyme immune and Bio-Plex assays, anti-HIV antibody titers were measured in stored serum samples collected at 3, 6, 9, 12, 24, 36, 48, and >48 months post-infection from 35 women assigned to TFV gel and 60 assigned to placebo gel, who acquired HIV during the trial. Additionally, anti-HIV antibody avidity maturation was assessed by the Bio-Rad avidity, and Bio-Plex assays. Kaplan Meier survival analysis and log rank test was used to determine differences between treatment arms. The slope and intercepts of the increase of antibody avidity or titer, as determined by the Bio-Plex assay, was compared. A linear mixed effects model was used to examine antibody titer and avidity by treatment group. Cox proportional hazard analysis examined time to avidity cut-off.

Results: Anti-HIV antibody titers, by both BED-CEIA and BioPlex assays did not differ between women assigned to TFV gel compared to those assigned to placebo gel. However, women assigned to TFV gel demonstrated slower antibody avidity maturation as determined by the Bio-Rad assay (p=0.04). In the Cox proportional hazard model, after adjustment for CD4 count and viral load, there was a significant reduction in the time to high avidity (HR=0.52, CI=0.32-0.84; p=0.008). For the Bio-Plex assay, there was a statistically significant slower increase in antibody avidity to gp120 (p=0.03) and a trend in gp160 (p=0.06) using a linear mixed effects model.

Conclusions: Women assigned to topical TFV had slower antibody maturation, similar to effects previously seen in TFV PrEP treated rhesus macaques. These results may have substantial public health implications for antibody-based incidence measurement as PrEP use increases globally.

988 Medication Sharing Among African HIV Serodiscordant Couples Enrolled in a PrEP Trial

Kerry A. Thomson[1]; Jessica Haberer[4]; Connie Celum[1]; Andrew Mujugira[1]; Patrick Ndase[1]; Craig Hendrix[2]; Mark A. Marzinke[2]; Allan Ronald[3]; David Bangsberg[4]; Jared Baeten[1]
On behalf of the Partners PrEP Study Team

[1]University of Washington, Seattle, MA, US; [2]Johns Hopkins University, Baltimore, MD, US; [3]University of Manitoba, Winnipeg, Canada; [4]Massachusetts General Hospital, Boston, MA, US

Background: Pre-exposure prophylaxis (PrEP) demonstrated high efficacy for HIV prevention among African HIV serodiscordant couples. One concern for PrEP implementation in all populations, and specifically for HIV serodiscordant couples, is the potential for PrEP medications to be shared with HIV-1 infected individuals. Drug sharing undermines PrEP efficacy for the HIV uninfected person prescribed PrEP and risks development of antiretroviral resistance in the HIV infected person who surreptitiously takes PrEP.

Methods: The Partners PrEP Study was a randomized placebo-controlled trial of daily oral tenofovir disproxil fumarate, alone or in combination with emtricitabine, among 4,747 African HIV serodiscordant couples. HIV infected partners were not eligible for or taking antiretroviral therapy (ART) at enrollment and were referred for ART during follow-up based on national ART eligibility guidelines. Self-reported data on sharing study drug tablets between study partners were collected from HIV uninfected partners at monthly study visits and from HIV infected partners annually. To examine biological evidence of drug sharing, tenofovir concentrations (>0.31 ng/mL) were measured in plasma collected at unannounced home visits from a random sample of 100 HIV infected partners not reporting ART.

Results: In 95,520 monthly study visits completed with HIV uninfected partners, there were three reports (0.003%) of drug sharing with their study partner; their HIV infected partner had taken a maximum of three study tablets in the prior month. In 5,605 annual visits with HIV infected partners, there was one (0.02%) report of taking one dose of the partner's study tablets. Tenofovir was detected in zero of 99 HIV infected partners at unannounced home visits (0%, 95% CI: 0-3.0%); one additional HIV-1 infected individual had an undetectable plasma HIV RNA concentration and tenofovir detected at enrollment and throughout follow-up, suggesting unreported use of tenofovir-containing combination ART rather than PrEP sharing.

Conclusions: In this clinical trial of PrEP, self-reported drug sharing appeared to be extremely rare and limited to HIV infected partners taking a small number of study pills during one study month. Plasma tenofovir testing supported the finding that sharing PrEP within HIV serodiscordant couples was uncommon. Concern about PrEP sharing should not be a limitation for PrEP implementation, although ongoing study outside of clinical trials is warranted.

THURSDAY, FEBRUARY 26, 2015

Session P-V6 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HIV Prevention, Miscellaneous

989 HIV-1 Transmission Risk Persists During the First 6 Months of Antiretroviral Therapy

Andrew Mujugira[1]; Katherine Thomas[1]; Connie Celum[1]; Deborah Donnell[2]; Carey Farquhar[1]; Elizabeth Bukusi[3]; Jared Baeten[1]
On behalf of the Partners PrEP Study Team

[1]University of Washington, Seattle, WA, US; [2]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [3]Kenya Medical Research Institute, Nairobi, Kenya

Background: Combination antiretroviral therapy (ART) decreases the risk of sexual HIV-1 transmission by suppressing HIV-1 RNA concentrations in blood and genital secretions to below undetectable levels. However, HIV-1 transmission may still occur prior to complete viral suppression.

Methods: Using data from a prospective study of heterosexual HIV-1 serodiscordant African couples (Partners PrEP Study, placebo arm), we quantified HIV-1 transmission risk in 3 time periods: between ART eligibility and treatment initiation, during the first 6 months of ART, and after more than 6 months of ART by when viral suppression is usually achieved. Sexual behavior, self-report of ART use by infected partners, and HIV-1 status of uninfected partners were assessed every 1-3 months. HIV-1 testing was performed using paired rapid antibody tests, with positive results confirmed by ELISA. The primary outcome was phylogenetically-linked HIV-1 transmission within the couple.

Results: We followed 496 uninfected members of serodiscordant couples for 510 person-years. The estimated proportion of unprotected sex acts was 8.1% between ART eligibility and ART initiation, 9.9% during the first 6 months of ART, and 10.8% during > 6 months of ART. HIV-1 incidence in couples eligible but not yet initiating ART was 1.71 per 100 person-years (95% CI: 0.35-5.01, 3 infections in 175 person-years). During the first 6 months after ART initiation, HIV-1 incidence was similar - 1.79 per 100 person-years (95% CI: 0.37-5.22, 3 infections in 168 person-years). There were no transmissions in 167 person-years after >6 months of ART (incidence rate, 0.00 per 100 person-years; 95% CI: 0.00, 2.20).

Conclusions: There was residual risk of HIV-1 transmission during the first 6 months after starting ART, as well as in couples who were eligible for ART but had not yet started treatment. For HIV-1 serodiscordant couples in which the infected partner is starting ART, or is eligible for ART but delays or declines therapy, other prevention options, such as antiretroviral pre-exposure prophylaxis, are needed, in addition to counseling to encourage ART initiation.

990 Long-Term ART Outcomes in Botswana Encouraging Treatment as Prevention Approach

Hermann Bussmann[4]; William C. Wester[1]; Ernest Fetogang[2]; Tony Chebani[2]; Sikhulile Moyo[3]; Naledi M. Mlaudzi[2]; Erik V. Widenfelt[3]; Joseph Makhema[3]; Max Essex[4]; Richard Marlink[4]

[1]Vanderbilt University School of Medicine, Nahville, TN, US; [2]Ministry of Health, Gaborone, Botswana; [3]Botswana Harvard AIDS Institute Partnership for HIV Research and Education, Gaborone, Botswana; [4]Harvard School of Public Health, Boston, MA, US

Background: Treatment as prevention (TasP) is currently the most promising HIV prevention strategy. Long-term adherence to TasP regimens and retention in care are critical to the success of this strategy. We herein report 10-year follow up among ART cohort participants initially enrolled in a 3-year randomized clinical trial (RCT) with two adherence strategies.

Methods: The Adult Antiretroviral and Drug Resistance (Tshepo) study was a 3-year randomized clinical trial (RCT) following 650 ART-naïve adults from Botswana who initiated certain first-line NNRTI-based ART. Participants were stratified by baseline CD4 count (bCD4 <=200 and 201-350 cells/μl) and randomized to 2 different adherence strategy arms. The RCT was completed in 2007 and participants were subsequently transferred to the Botswana national ART program. Ten-year outcome data was abstracted from the national ART program.

Results: 650 adults enrolled between 2002-2004, 451 (69.4%) of which were female. Forty-three percent had advanced WHO clinical disease (3 or 4) at enrollment. Median age and BMI [IQR] was 33.3 years [IQR 28.9 – 38.7] and 21.3 [19.2-24.3], respectively. During 3-year RCT follow-up 35 (5.4%) of 650 patients had at least one ART switch due to virologic failure at a mean 68.7 weeks (STD 33.3) and 37 (5.7%) of 650 patients died. As of March 2014, 538 (83%) patients were still receiving ART (mean duration of ART = 8.4 years); of these 268 (83.8%) had bCD4 <=200 and 270 (81.8%) had bCD4 201-350 (p=0.541). 172 (26.5%) of 650 patients had at least one confirmed virologic failure (VF) (Viral load>1000) at median 3.5 years (IQR 1.5 to 6.4); crude VF rate 4.2/100PY. Fifty-six (8.6%) patients had died at median 1.4 years (IQR 0.6 to 4.4); crude mortality rate of 1.2/100PY. Eighty-one (12.5%) of 650 patients were not traceable (unknown F/U status). There was no difference among cases of unknown F/U status or death by adherence arm, age strata and/or sex. As of 2014, among those receiving first-line ART, 50.3% were receiving TDF-based ART most others receiving ZDV/3TC-based regimens. More than one-third (38.7%) had been switched to 2nd or 3rd line protease inhibitor therapy-based ART.

Conclusions: In summary, at greater than 10 years after enrollment, adult patients in a public ART program which emphasized education and lab monitoring, had excellent survival and retention (83%) years after completing a RCT. These results are encouraging for both the patients and for the potential impact of TasP in this setting.

991LB Use of Population Viral Load to Predict HIV-Incidence in a Hyperendemic Population in Rural KwaZulu-Natal, South Africa

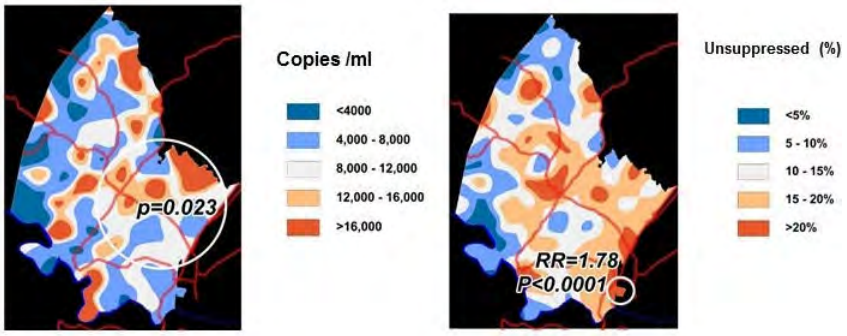
Frank Tanser[3]; Tulio de Oliveira[3]; Till Barnighausen[2]; Deenan Pillay[1]

[1]University College London, London, United Kingdom; [2]Harvard School of Public Health, Boston, MA, US; [3]University of KwaZulu-Natal, Mtubatuba, South Africa

Background: *Population viral load* is argued to be a good measure of HIV transmission potential in a population. However, calculation of this measure rarely includes HIV-infected individuals who have not accessed the health system for HIV diagnosis and treatment. Further, such approaches have not been applied to hyperendemic populations in Southern Africa. Here we provide results from a *population viral load* survey covering an entire population in a hyperendemic community participating in annual HIV testing in rural KwaZulu-Natal, South Africa.

Methods: The study uses data from one of the most comprehensive demographic surveillance sites in Africa - the Africa Centre Demographic Information System. The site has conducted population-based HIV testing for over a decade. HIV testing takes place annually in all consenting resident individuals' ≥15 years of age. We performed viral load measurements on blood-spots collected from all 2,420 individuals testing HIV positive in the population-based HIV testing. All individuals were geolocated to their exact homestead of residence. We used a two-dimensional Gaussian kernel of radius 3km to map viral suppression, geometric mean population viral load and dcalculated an index of transmission potential termed the *population prevalence of detectable virus* (PPDV) - proportion of the entire population (ie irrespective of HIV status) having a detectable viral load. We then followed up 11, 806 HIV-negative individuals and quantified in multi-variable survival analysis the effect of PPDV in the surrounding local community on the risk of HIV acquisition.

Results: Overall median viral load was 6428 copies per ml. 30% (726) of all HIV positive individuals in the population were below the detectable limit for blood spots of 1550 copies/ml. Marked spatial heterogeneity in geometric mean population viral load (Figure 1a) and PPDV (Figure 1b) occurred across the surveillance area with clear evidence of spatial clustering of high viral loads. Every 1% increase in community level PPDV was independently associated with a 4% increase in individual risk of acquisition of infection (HR= 1.04, p<0.001).



Geographical variations in geometric mean population viral load (a) and population prevalence of detectable virus [PPDV] (b) in 2011 derived by a two-dimensional standard Gaussian kernel of radius 3km. Formal spatial clusters of high viral loads (a) or high proportion of individuals with unsuppressed viral loads (b) identified by the Kulldorff spatial scan statistic are superimposed.

Conclusions: Our findings reveal remarkable spatial variation in *population viral load* in this relatively homogenous population. The results show that even in a severely affected rural African population with a well-established HIV treatment programme, PPDV could play a role in targeting interventions to specific communities to reduce the overall rate of new infections.

992LB Phase 1 Safety & PK Trial of Polyurethane Tenofovir Disoproxil Fumarate Vaginal Ring

Marla J. Keller[1]; Pedro Mesquita[1]; Mark A. Marzinke[2]; Ryan Teller[3]; Bruce Frank[4]; Mark Mitchnick[4]; Peter L. Anderson[5]; Craig Hendrix[2]; Patrick F. Kiser[3]; Betsy Herold[1]

[1]Albert Einstein College of Medicine, Bronx, NY, US; [2]Johns Hopkins University School of Medicine, Baltimore, MD, US; [3]Northwestern University, Evanston, IL, US; [4]Particle Sciences, Inc, Bethlehem, PA, US; [5]University of Colorado, Aurora, CO, US

Background: The prodrug tenofovir disoproxil fumarate (TDF) is more potent than tenofovir (TFV) against HIV *in vitro* & has greater tissue permeability & cellular uptake. Sustained TDF delivery from a vaginal ring (VR) completely protected macaques from multiple vaginal simian-HIV challenges. The objectives of this trial were to evaluate safety & PK of reservoir-type TDF & placebo polyurethane VRs when used continuously for 14 days (d).

Methods: A randomized, single blind, placebo controlled trial of 30 women was conducted. Clinical safety was assessed. Swabs (2 proximal, 1 distal to VR) & plasma were collected 1, 3, 7 & 14 d after VR insertion & 2 & 7 d after removal for drug levels. Dried blood spots (DBS) were obtained after 7 & 14 d of VR use. Cervical tissue was collected for TFV, TFV-diphosphate (TFV-DP) & *ex vivo* HIV challenge studies. Tissue HIV LTR DNA in relative copy number was quantified by real-time PCR. To measure anti-HIV activity of luminal drug, Jurkat-Tat-CCR5 cells were challenged *ex vivo* with HIV-1_{BaL} in the presence of cervical swab eluants. p24 levels in supernatants were assessed by AlphaLISA.

Results: 29 of 30 women completed the study (15 TDF, 14 placebo). The mean age was 29.7 years. There were 43 adverse events; 8 were product related & were Grade 1. Median TFV vaginal fluid (VF) levels in 10 women at 1, 3, 7 & 14 d after VR insertion were 4, 5, 7 & 7.3 x 10^4 ng/mL, respectively. Only 1 had detectable TFV-DP by DBS after 7 d but 11 of 14 had detectable levels after 14 d of TDF VR use (range 37-335 fmol/punch). Tissue TFV-DP levels in 10 women ranged from 52-550 fmol/mg. Tissue from women in TDF arm challenged *ex vivo* had a 90% reduction in HIV copy number compared to no change in the placebo arm ($p<0.0001$, Mann Whitney). Compared to baseline, cervical swab eluants significantly inhibited HIV replication at 7 ($p=0.002$) & 14 d ($p=0.01$, Wilcoxon matched-pairs signed rank test) after VR use in TDF group, which correlated significantly with cervical swab TFV levels ($r=0.52$, $p=0.01$, Spearman correlation). Tissue TFV-DP levels were greater after VR use than those observed after oral TDF in the highly effective Partners PrEP trial, but less than levels achieved after TFV gel dosing (Table).

Study	Drug & Dosing	Relative Risk Reduction mean, 95% CI	Plasma TFV ng/mL median, IQR	Tissue TFV-DP fmol/mg median, IQR
Partners PrEP	TDF oral daily	0.67 (0.44-0.81)	70 (33-111)	Not determined
MTN 001 (US)	TDF oral daily	Phase 1	88 (15-103)	2.5 (10-25)
MTN 001 (US)	TFV gel daily	Phase 1	1.8 (BLQ-2.0)	1807 (591-5860)
U19	TDF **ring**	Phase 1	In progress	117 (86-185)

Conclusions: A TDF VR is safe, well tolerated & resulted in TFV VF levels that exceed the clinical correlate of protection observed with TFV gel BAT24 dosing. TFV-DP detected in DBS suggests that it may provide a sensitive maker of adherence. Findings support further development of this TDF VR.

993 Investigating the Pharmacokinetics of Rectal 1% Tenofovir Gel in Rhesus Macaques

Charles W. Dobard[1]; Andrew Taylor[1]; Chuong Dinh[1]; Chou-Pong Pau[1]; Ian McGowan[2]; Lisa Rohan[2]; Walid Heneine[1]

[1]Centers for Disease Control and Prevention, Atlanta, GA, USA, Atlanta, GA, US; [2]University of Pittsburgh Magee-Womens Research Institute, Pittsburgh, PA, US

Background: Rectally formulated gels containing antiretroviral (ARV) drugs are under development to prevent rectal HIV transmission. Efficacy of ARV gels will likely depend on efficient drug release and absorption through the rectal mucosa. However, little is known on how gel volumes and physiological barriers such as feces and mucus may affect drug absorption. This study evaluated pharmacokinetics of different volumes of 1% TFV gel in a macaque model and investigated the effect of feces and mucus on systemic drug absorption.

Methods: 1% TFV was formulated in a rectal specific hydrogel based formulation. The formulation was designed to have neutral pH (7) and be close to iso-osmolar (479±6 mOsmol/kg). The effect of gel volume on systemic TFV absorption was investigated in macaques (n=6) receiving 4, 1, and 0.5 mL of 1% TFV gel. Gel application was followed by measurements of plasma TFV levels at 0.5, 2, 6, and 24 hours by HPLC MS/MS. The Cmax and area under the curve (AUC) values were measured over 24h. The impact of feces and mucus on drug absorption was evaluated by comparing Cmax and AUC values among macaques (n=6) that underwent extensive rectal washes with saline (5 total washes) and unwashed animals (n=6) prior to receiving 4 ml of rectal gel. In all macaques, fecal presence prior to gel dosing, was monitored using pre-moistened rectal swabs.

Results: Peak plasma TFV levels were detected at 30 minutes with all gel volumes. In contrast, AUCs and C_{max} values increased proportionally with gel volume. With 4 ml of gel, Cmax and AUC values were 42 ng/ml and 121 ng*h/ml, respectively. These values decreased to10 ng/ml and 37 ng*h/ml with the 1 ml dose, and to 3.8 ng/ml and 7.5 ng*h/ml/h with the 0.5 ml dose. A dose response analysis showed that 1 ml of gel recapitulates systemic TFV levels seen with 4 ml of 1% TFV gel applied rectally in humans (Cmax= 8 ng/ml and AUC=52 ng*h/ml/h). Rectal washes significantly increased systemic TFV absorption compared to unwashed ($AUC_{0\text{-}24h}$ = 120.15 and 50.25 ng*h/mL, respectively; p=0.01).

Conclusions: In this macaque model, dose proportionality was observed between the lowest and highest gel volume of this TFV rectal gel formulation and included a dose that recapitulates the *in vivo* release and systemic TFV absorption achieved in humans. The higher TFV absorption seen following rectal washes reflects increased mucosal exposure and suggests that cleansing practices prior to gel application may increase TFV exposure in humans.

994 CHARM-01, a Phase 1 Rectal Safety, Acceptability, PK/PD Study of 3 Tenofovir Gels

Ian McGowan[1]; Kathy Duffill[2]; Charlene Dezzutti[1]; Nicola Richardson-Harman[3]; Mark A. Marzinke[4]; Ross D. Cranston[1]; Lisa Rohan[1]; Craig W. Hendrix[4]; Julie Elliott[5]; Peter Anton[5]

[1]University of Pittsburgh, Pittsburgh, PA, US; [2]Magee-Womens Research Institute, Pittsburgh, PA, US; [3]Alpha StatConsult LLC, Damascus, MD, US; [4]Johns Hopkins University School of Medicine, Baltimore, MD, US; [5]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US

Background: Three formulations of tenofovir (TFV) gel have been evaluated in clinical trials and it is uncertain which gel formulation should be developed as a rectal microbicide. The CHARM-01 study was undertaken to characterize the rectal safety, acceptability, pharmacokinetics (PK), and pharmacodynamics (PD) of three TFV gels: a vaginal formulation (VF), a reduced glycerin vaginal formulation (RGVF), and a rectal formulation (RF) with osmolalities of 3111, 846, and 479 mOsmol/kg respectively. The VF gel was previously used in the CAPRISA 004 and VOICE vaginal microbicide Phase 2B trials. The VF gel was used in the RMP-02/MTN-006 Phase 1 rectal safety study. The RGVF gel was used in the MTN-007 Phase 1 rectal microbicide trial and is currently being evaluated in the MTN-017 Phase 2 rectal microbicide trial.

Methods: Participants received 4 mL of the three TFV gels in a blinded, crossover design and received in a randomized sequence: (i) 6 daily doses of a HEC placebo followed by a final single dose of the VF gel, (ii) 7 daily doses of the RGVF gel, and (iii) 7 daily doses of the RF gel. Safety, acceptability, compartmental PK, and explant PD were monitored throughout the trial.

Results: A total of thirteen participants were enrolled into the CHARM-01 study at two sites in Los Angeles and Pittsburgh. All three gels were found to be safe and acceptable. Median rectal tissue homogenate TFV-diphosphate (DP) concentration was significantly greater with the RF (10.3 ng/mg) versus the VF (below the limit of quantification) gel ($p \leq 0.05$). Median mucosal mononuclear cell (MMC) TFV-DP was significantly greater with the RF (1136 fmol/10^6 cells) versus RGVF (320 fmol/10^6 cells) gel ($p \leq 0.05$). Use of each gel *in vivo* was associated with significant inhibition of *ex vivo* colorectal explant HIV infection. There was also a significant negative correlation between the tissue levels of TFV, tissue TFV diphosphate (DP), MMC TFV-DP (Figure 1), rectal fluid TFV, and explant HIV-1 infection.

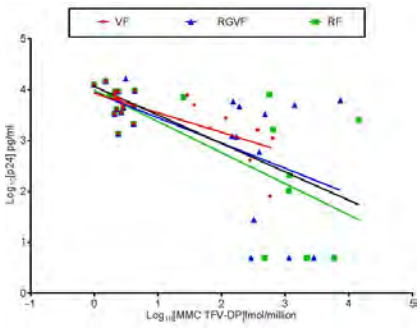


Figure 1: Pharmacokinetic / Pharmacodynamic relationship between mucosal mononuclear cell concentrations of TFV-DP and colorectal explant supernatant HIV-1 p24 levels (overall $P < 0.0001$)

Conclusions: All three formulations were found to be safe and acceptable. There was a trend towards higher tissue levels of TFV associated with exposure to the RF gel. Exposure to all three gels was associated with significant inhibition of explant infection. There was a significant negative correlation between compartmental PK and explant infection. Based on these data, either the RGVF or the RF gel could be advanced into later stage development as a candidate rectal microbicide.

995 Female Condom Functionality in the Presence of a Vaginal Ring

Annalene M. Nel[1]; Mildie Leuvennink[1]; Neliette Van Niekerk[1]; Terri Walsh[2]; Ron Frezieres[2]

[1]International Partnership for Microbicides, Paarl, South Africa; [2]California Family Health Council Inc, Los Angeles, CA, US

Background: IPM is evaluating the safety and efficacy of a dapivirine vaginal ring for the prevention of HIV-1 acquisition through male to female transmission. Once the safety and efficacy of the dapivirine vaginal ring have been proven, it should be fully compatible with concurrent use of male and female condoms. The functionality of female condoms (FCs) with the vaginal ring was evaluated.

Methods: The total clinical failure rate of FCs in the presence and absence of a placebo vaginal ring was assessed in an open-label, randomized, two-period, crossover non-inferiority trial. Eighty-one healthy, monogamous, heterosexual couples, aged 18-55 years, were enrolled. Each couple used 4 study FCs when the female was wearing the vaginal ring and 4 study FCs when the female was not wearing the ring. The total clinical failure rate was defined as the number of FCs with breakage, complete slippage, misdirection or invagination during intercourse, divided by the number of FCs used. The safety, tolerability and acceptability of FCs in the presence of the vaginal ring and the frequency of ring expulsion or removal were assessed.

Results: 297 FCs were used with the vaginal ring and 299 FCs without the ring. The total clinical failure rate was 14.1% with the vaginal ring and 15.7% without the ring. The difference "with ring–without ring" was -2.1% (95% CI: -7.8%; 3.6%). The upper bound of the CI was less than the pre-defined non-inferiority margin of 8%. No clinical breakage during intercourse was reported with or without the ring. Five adverse events (AEs) were reported: genital burning sensation (1 male), pelvic discomfort, bacterial vaginitis and two events of vulvovaginal discomfort (4 females). Two product-related AEs were reported (Grade 1): bacterial vaginitis (with ring) and vulvovaginal discomfort (without ring). No serious AEs were reported; no AE led to trial discontinuation. Use of the vaginal ring resulted in more couples feeling the vaginal ring or FC inner ring, more movement of these rings during intercourse and more interference of the rings with intercourse, which increased the odds of them being bothered by the vaginal ring, affecting sexual satisfaction.

Conclusions: Female condom use was safe with vaginal ring use. The presence of the vaginal ring did not negatively affect the total clinical failure rate of FCs. No ring expulsions or removals during intercourse were reported.

TUESDAY, FEBRUARY 24, 2015

Session P-W1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

HIV Testing and the Continuum of Care in the Industrialized World

996 Continuous Retention Predicts Viral Suppression Across the US and Canada

Peter F. Rebeiro[1]; Baligh R. Yehia[2]; Kelly Gebo[3]; Bryan Lau[3]; Kenneth H. Mayer[4]; Michael A. Horberg[5]; Mari Kitahata[6]; John Gill[7]; Timothy Sterling[1]; Stephen J. Gange[3]
North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)

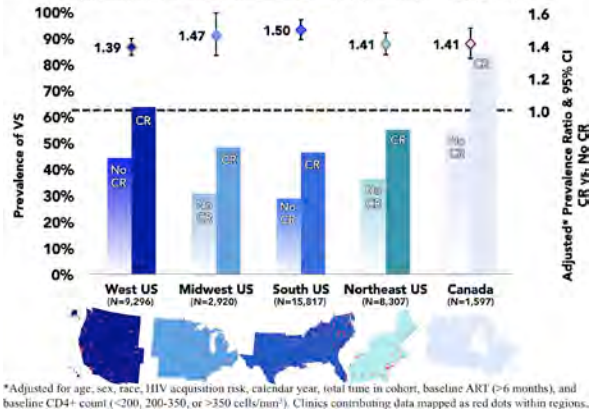
[1]Vanderbilt University, Nashville, TN, US; [2]University of Pennsylvania, Philadelphia, PA, US; [3]Johns Hopkins University, Baltimore, MD, US; [4]Harvard University, Boston, MA, US; [5]Mid-Atlantic Permanente Research Institute, Kaiser Permanente Mid-Atlantic States, Rockville, MD, US; [6]University of Washington, Seattle, WA, US; [7]University of Calgary, Alberta Health Services, Calgary, Canada

Background: Retention in care is an HIV care continuum priority. We examined the association between continuous clinical retention (CR) and HIV viral suppression (VS) and evaluated whether this association was similar across geographic regions in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), a large, geographically diverse HIV cohort collaboration in the US and Canada.

Methods: Adults with ≥2 HIV primary care visits ≥5 years apart from 2000-2012 in NA-ACCORD clinical cohorts were classified as CR if they had ≥2 visits within each calendar year, >90 days apart (the US National HIV/AIDS Strategy indicator). Patients' CR status was assigned for their first 5 years in the cohort. Individuals were assigned to US Centers for Disease Control and Prevention-defined regions or to Canada based on state/province-level residential (12 cohorts) and clinic (2 cohorts) location. VS was defined as an HIV-1 RNA <200 copies/mL at last measurement in the last semester. The prevalence of VS was estimated and the association with CR quantified with prevalence ratios (PR)s using modified Poisson regression both overall and by region. Age, sex, race/ethnicity, HIV acquisition risk, baseline CD4+ count, and baseline ART were adjusted for as potential confounders of the CR-VS relationship.

Results: Among 37,937 adults contributing 189,685 person-years of follow-up, 38% experienced CR (41% in the Northeast, 43% in the Midwest, 36% in the South, 35% in the West, and 38% in Canada), and CR was significantly associated with increased prevalence of VS (PR=1.41 vs. no CR, p<0.05). The prevalence of VS among those with CR was highest in the West and Canada (68% and 85%, respectively) and lowest in the South (46%), though the influence of CR on VS was of similar strength within every region (p>0.05, Figure).

Figure: Prevalence (bars), adjusted prevalence ratio estimates (diamonds), and 95% confidence intervals (CI) for HIV viral suppression (VS), conditional on continuous retention (CR), within regions of the US and Canada.



*Adjusted for age, sex, race, HIV acquisition risk, calendar year, total time in cohort, baseline ART (>6 months), and baseline CD4+ count (<200, 200-350, or >350 cells/mm³). Clinics contributing data mapped as red dots within regions.

Conclusions: These data demonstrate strong benefits of continuous HIV care, regardless of cultural and geographic differences. Further, despite widespread availability of therapy, these results demonstrate continued improvements are needed in optimizing delivery and care for HIV-infected individuals to translate viral reductions to the population level.

997 Disparities in HIV Viral-Load Suppression Among MSM, the HIV Outpatient Study, 2013

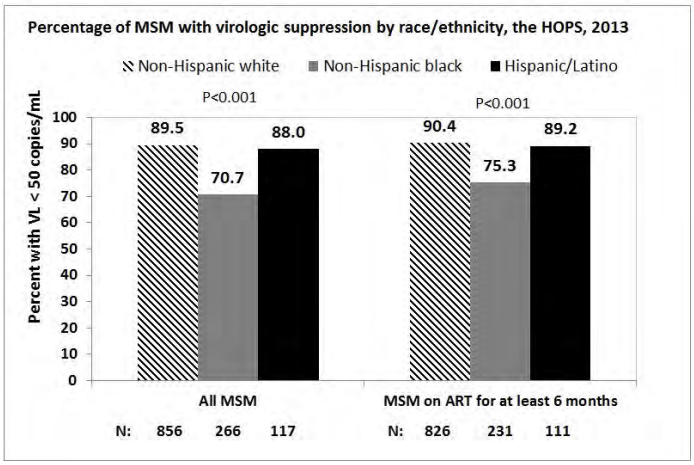
Kate Buchacz[1]; Carl Armon[2]; Ellen Tedaldi[3]; Frank J. Palella[4]; Richard Novak[5]; Doug Ward[6]; Benjamin Young[7]; Rachel Debes[2]; Marcus Durham[1]; John T. Brooks[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]Cerner Corporation, Vienna, VA, US; [3]Temple University School of Medicine, Philadelphia, PA, US; [4]Northwestern University, Chicago, IL, US; [5]University of Illinois at Chicago, Chicago, IL, US; [6]Dupont Circle Physicians Group, Washington, DC, US; [7]International Association of Providers in AIDS Care, Washington, DC, US

Background: The National HIV/AIDS Strategy has prioritized reducing disparities in virologic suppression (VS) by race/ethnicity among gay, bisexual and other men who have sex with men (collectivey referred to as MSM). Improving VS for black MSM may decrease HIV morbidity and sexual transmission of HIV.

Methods: We analyzed data from the HIV Outpatient Study (HOPS) MSM participants in care at 9 HIV specialty clinics in the United States. We limited analyses to MSM with ≥ 2 HOPS visits since HOPS inception in 1993, of which at least one occurred in 2013, and who were of non-Hispanic white (NHW), non-Hispanic black (NHB) or Hispanic/Latino race/ethnicity (Hispanic). We assessed the frequency of VS, defined as an HIV RNA (viral load, VL) < 50 copies/mL, measured closest but prior to 31 December 2013 among all MSM and those prescribed ART for ≥ 6 months. Using logistic regression, we assessed factors associated with VS among MSM prescribed ART.

Results: Among 1,239 MSM studied, 266 (21%) were NHB, and 117 (9%) were Hispanic. NHB MSM were younger than NHW and Hispanic MSM (median age 43 vs. 51 and 45 years, respectively), more frequently HIV-diagnosed after 2006 (35% vs. 14% and 23%), less frequently privately insured (36% vs. 71% and 53%) and more frequently cared for at public rather than private clinics (66% vs. 14% and 39%) all $p < 0.001$. The median nadir and current CD4 cell counts (cells/mm^3) were: for NHB, 242 and 532; for NHW, 235 and 628; and for Hispanics, 207 and 576. Fewer NHB MSM were prescribed ART at the time of VL measurement (92% vs. 98% and 97%) and VS was less common among NHB than NHW and Hispanic MSM, $p < 0.001$ (Figure). In analyses restricted to MSM prescribed ART, which adjusted for clinic type and demographic and clinical factors, NHB MSM had lower odds of VS than NHW (odds ratio [OR] 0.54, 95% confidence interval [95% CI] 0.35-0.84) but Hispanic MSM did not (OR 1.22, 95% CI 0.63-2.37); MSM seen in public clinics had lower odds of VS (OR 0.48, 95% CI: 0.32-0.73) than those seen in private clinics, and MSM with higher CD4+ cell counts had higher odds of VS (OR, 1.19 per 100 cells/mm^3, 95% CI: 1.11-1.27); insurance type was not independently associated with VS.



Conclusions: In our large heterogeneous HIV cohort, NHB MSM had significantly lower rates of VS than NHW and Hispanic MSM. The associations of race/ethnicity and clinic type with VS suggest that interventions to improve HIV care outcomes for all MSM may need to address structural factors and social disparities.

998 Early Linkage to HIV Care and Antiretroviral Therapy Use Among People Who Inject Drugs: 20 US Cities, 2009 and 2012

Brooke Hoots; Teresa Finlayson; Dita Broz; Gabriela Paz-Bailey

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: Approximately 16% of infections among those living with diagnosed HIV infection are attributable to injection drug use. Antiretroviral therapy (ART) is recommended for all infected persons to improve health and prevent transmission. Timely linkage to care is a key step for ART initiation. One goal of the National HIV/AIDS Strategy is to increase early linkage to care from 65% to 85% by 2015. Using data from the National HIV Behavioral Surveillance System, we evaluated changes in early linkage to care and ART use from 2009 to 2012 among persons who inject drugs (PWID).

Methods: PWID were recruited by respondent-driven sampling in 20 cities in 2009 and 2012. Early linkage was defined as a clinic visit for HIV care within 3 months of diagnosis and ART use as use at time of interview. Analyses were restricted to PWID with a previous HIV-positive test. Early linkage models were restricted to those diagnosed with HIV ≥ 3 months prior to interview. We used log-linked Poisson GEE regression to examine differences in the outcomes between 2009 and 2012. Models were adjusted for year, city, peer network size, gender, race/ethnicity, education, and insurance; the early linkage model included age at diagnosis, and the ART model included current age. Interaction terms were included to explore demographic variations.

Results: Early linkage to care was 57% (285/504) in 2009 and 62% (353/569) in 2012 ($P = .07$). In both years, early linkage was higher among those with an older age of diagnosis (>25) and those with insurance. In a multivariable model, early linkage did not change overall ($P = .61$) and only increased significantly for whites ($P = .05$). ART use was 58% (319/548) in 2009 and 67% (410/608) in 2012 ($P = .001$). In both years, greater ART use was observed among males, blacks, older age groups, and those with insurance. In a multivariable model, ART use significantly increased from 2009 to 2012 ($P = .03$). ART use also increased among females ($P = .04$), Hispanics ($P = .003$), and those with less education ($P = .02$). Despite the increase among females, males were 18% more likely to be on ART when data from both years were combined ($P = .0017$).

Conclusions: While early linkage to care among PWID did not increase significantly between 2009 and 2012, ART use did. These findings show progress in getting those in care on treatment. Strengthening intervention efforts among PWID may improve early linkage to care and coverage of ART in this population.

999 Late HIV Diagnosis in Metropolitan Areas of the United States and Puerto Rico

H. Irene Hall[1]; Tian Tang[2]; Lorena Espinoza[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]ICF International, Atlanta, GA, US

Background: The majority of persons diagnosed with HIV are residents of large metropolitan areas and many large metropolitan areas have implemented intensified HIV testing programs. Yet many persons are diagnosed with late stage disease (stage 3, AIDS).

Methods: Using data reported through December 2013 from the National HIV Surveillance System, we determined the percentage of persons diagnosed with late stage disease (stage 3 based on CD4 count <200 cells/mL or opportunistic illness within 3 months of HIV diagnosis) among persons diagnosed with HIV during 2012 in metropolitan statistical areas (MSAs) (population ≥500,000, including individual MSAs; and population 50,000 to 499,999) and non-metropolitan areas. We also determined trends in late diagnosis from 2003-2012 and assessed change using linear regression. Data were statistically adjusted for missing HIV transmission categories.

Results: Overall, 24% of persons diagnosed in 2012 in the Unites states had a late diagnosis; 23.3% in large MSAs, 26.3% in small to medium MSAs, and 29.7% in non-metropolitan areas. In the 105 large MSAs, the percentage diagnosed late ranged from 13.5% in Birmingham-Hoover, AL to 44.4% in Modesto, CA. In large MSAs, overall the percentage diagnosed late was 22.7% for blacks/African Americans, 24.7% for Hispanics/Latinos, and 23.1% for whites; however, in some MSAs a higher percentage of blacks/African Americans was diagnosed late compared with Hispanics/Latinos or whites (e.g., New York MSA, 23.9%, 20.8%, 18.2%, respectively). In the majority of large MSAs, persons with infection attributed to male-to-male sexual contact had a lower percentage diagnosed late compared to persons with infection attributed to injection-drug use or heterosexual contact. During 2003-2012, the percentage diagnosed late decreased in large MSAs (32.2% to 23.3%), smaller MSAs (33.4% to 26.3%), and non-metropolitan areas (33.3% to 29.7%); however, the percentage remained stable since 2008 in non-metropolitan areas. Significant decreases (P<0.01) occurred in 41 of 105 large MSAs overall and among men who have sex with men.

Conclusions: During the past decade, the percentage of persons with a late HIV diagnosis decreased overall and in many individual areas with high HIV burden. However, even in areas with intensified HIV testing interventions, about 1 in 5 persons were diagnosed with advanced disease. In addition, there are disparities by race/ethnicity and transmission risk group in some areas.

1000 HIV Care During the Last Year of Life

H. Irene Hall[1]; Lorena Espinoza[1]; Shericka Harris[2]; Jing Shi[2]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]ICF International, Atlanta, GA, US

Background: Death due to HIV remains a leading cause of death among some U.S. populations, in particular among persons aged 25 to 44 years old and blacks/African Americans. Little information is available about HIV care and care outcomes at the end of life among persons living with HIV.

Methods: We used data from the National HIV Surveillance System to determine disease stage and care received within 12 months prior to death among persons living with HIV who died in 2012. Data were available from 18 U.S. jurisdictions on CD4 and viral load test results. Persons were considered to be in care within the 12 months before death if they had one or more CD4 or viral load test results, and in continuous care if they had two or more CD4 or viral load test results at least 3 months apart. Viral suppression (defined as <200 copies/mL) was based on the most recent viral load test result in the 12 months before death. Data were statistically adjusted for missing HIV transmission categories.

Results: Among 6,932 persons infected with HIV who died in the 18 jurisdictions, 47.5% had disease classified as stage 3 (AIDS) within 12 months before death; 13.8% had stage 1 (CD4 count ≥500 cells/μL), 22.5% stage 2 (CD4 count 200–499 cells/μL), and 16.2% unknown stage disease. Overall, 86.3% had ≥1 test result, 64.7% had ≥2 tests at least 3 months apart, and 42.3% had a suppressed viral load. While blacks/African Americans and Hispanics/Latinos had higher percentages of continuous care compared with whites, (65.5%, 67.4% and 60.1%, respectively), they had lower percentages of viral suppression (36.3%, 44.2% and 49.3%, respectively) and higher percentages with late stage disease (50.9%, 51.9%, and 39.1%, respectively). The percentage in continuous care was somewhat higher and the percentage with viral suppression was substantially higher among older persons compared with those aged 20-29 years (e.g., 20-29 vs. ≥65 year olds, ≥2 test results, 59.5% vs. 65.4%; viral suppression, 21.1% vs. 52.4%). Viral suppression was similar among the 83.6% of persons who ever had late stage disease (stage 3, AIDS) (42.5%) compared with those never diagnosed with AIDS (41.1%).

Conclusions: The majority of persons infected with HIV who died in 2012 had HIV medical care visits in the year before death. However, almost half of them had late stage disease, and late stage disease and lack of viral suppression was more common among blacks/African Americans and Hispanics/Latinos and younger persons.

1001 Reductions in the Time From HIV Infection to ART Initiation in New York City

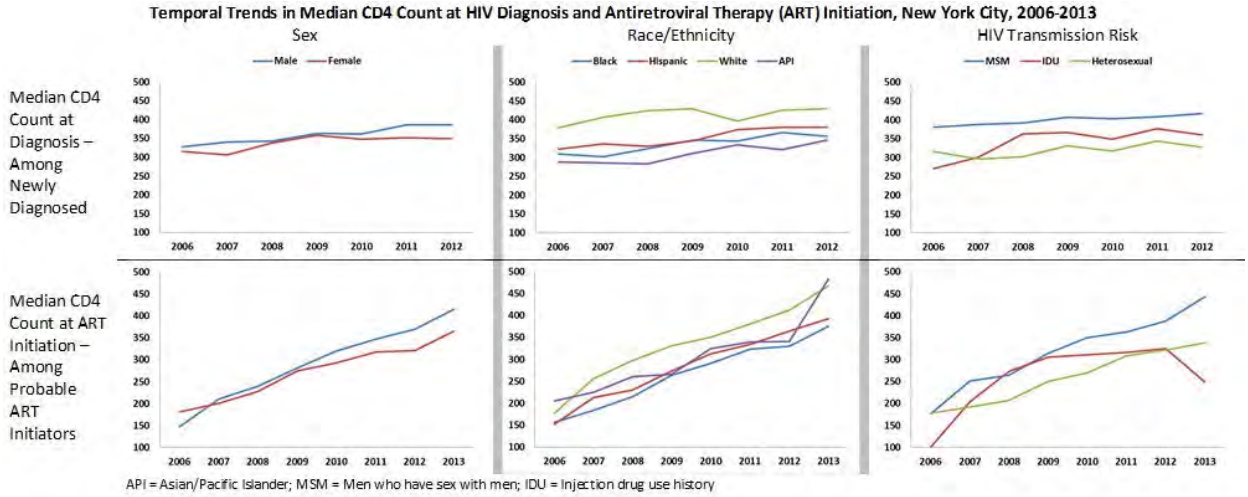
Sarah L. Braunstein[1]; McKaylee Robertson[2]; Julie Myers[1]; Bisrat Abraham[3]; Denis Nash[4]

[1]New York City Department of Health and Mental Hygiene, Queens, NY, US; [2]City University of New York, New York, NY, US; [3]Weill Cornell Medical College, New York, NY, US; [4]City University of New York School of Public Health, New York, NY, US

Background: Many state and local jurisdictions in the US, including New York City (NYC), support implementation of national recommendations for immediate ART initiation among persons diagnosed with HIV (PWH) and have implemented geographically targeted HIV testing campaigns to facilitate earlier HIV diagnosis. We used population-based data on CD4 cell count at HIV diagnosis and ART initiation to estimate the rate at which efforts aimed at earlier diagnosis and ART initiation are progressing.

Methods: We used laboratory (CD4, viral load (VL)) data reported to NYC HIV Surveillance on PWH age ≥13 years diagnosed during 2006-2012. The CD4 count at diagnosis was the first CD4 count within 6 months of diagnosis; we estimated the date of probable ART initiation following HIV diagnosis to be the mid-point between two VLs bracketing the first occurrence of: 1) a ≥2-log drop in a 3 month period; or 2) a detectable VL followed by an undetectable VL (<400 copies/mL). The CD4 count at ART initiation was defined as that closest to and within 3 months of the estimated date of ART initiation.

Results: A total of 24,358 persons were newly diagnosed with HIV in NYC from 2006-2012. Of these, 17,773 (73%) had a CD4 count within 6 months of diagnosis, and 14,051 (79%) of those persons had probable ART initiation during 2006-2013. 12,809 (91%) of those initiating ART had a CD4 count within 3 months of the date of probable ART initiation. The overall median CD4 count at diagnosis increased from 325 cells/μL in 2006 to 379 cells/μL in 2012 (average: 7.7 cells/year), while the median CD4 count at ART initiation increased from 157 cells/μL in 2006 to 410 cells/μL in 2013 (average: 31.6 cells/year). All demographic and risk subgroups experienced increases in CD4 at diagnosis and ART initiation during 2006-2013, although increases were substantially slower among some subgroups (Figure). In 2012, only half of PWH were diagnosed at CD4 count >379 cells/μL; 53% of persons who initiated ART in 2012 were diagnosed that year.



Conclusions: Surveillance data indicate that the time from HIV infection to ART initiation has been substantially reduced among newly diagnosed NYC PWH. Slower improvements in the median CD4 at diagnosis relative to that at ART initiation highlight the need for additional progress in earlier HIV diagnosis and care linkage. Use of CD4 as a time-sensitive metric can complement the HIV care continuum and help target and evaluate efforts aimed at earlier diagnosis and ART initiation.

1002 Return to HIV-Related Medical Care After a Hiatus of ≥1 Year, New York State, 2013

Carol-Ann Swain[4]; Daniel Gordon[4]; Jessica L. Simpson[3]; Bridget J. Anderson[4]; Bruce D. Agins[1]; Lou C. Smith[2]

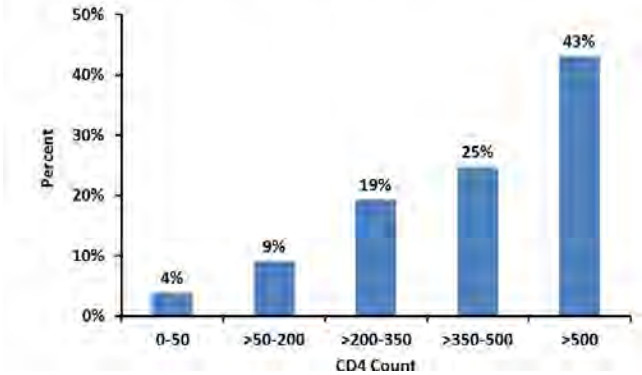
[1]Office of the Medical Director, New York State Department of Health, New York, NY, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [3]Division of Epidemiology, Evaluation and Research, New York State Department of Health, Albany, NY, US; [4]New York State Department of Health, Albany, NY, US

Background: Engagement in HIV medical care results in greater access to antiretroviral therapy, faster HIV viral suppression and better health outcomes among HIV positive persons. In New York State (NYS) one third of HIV-diagnosed persons had no evidence of care in 2012. The study goal was to identify factors associated with receipt of HIV-related medical care in 2013 among a cohort of persons with no laboratory indication of care in 2012.

Methods: NYS HIV surveillance data as of April 2014 were restricted to persons aged ≥13 years, diagnosed 2006-2010 in NYS, linked to care within one year of diagnosis and living as of December 2013. Out of care status was defined as having no reported HIV-related test in 2012; return to care was defined as having an HIV-related test in 2013. Risk ratios (RR) and 95% confidence intervals (CI) for return to care were calculated using a log binomial multivariate model adjusted for: viral load at last test, race/ethnicity, age, HIV transmission risk, year of diagnosis, year of last reported test and country of birth.

Results: 15,261 persons met the inclusion criteria; 2,997 (20%) had no care in 2012. The no-care group was predominately male (75%), non-Hispanic black (47%), and had MSM (men who have sex with men) transmission risk (45%). 55% of the no-care group had had a test in 2010 or 2011, but 11% had no test after 2007. 13% met the CDC AIDS case definition (CD4 count <200 cells/mm3) at last test before reengagement (Figure) and 62% were not virally suppressed (>200 copies of HIV/ml). 535 (18%) persons returned to care in 2013. In multivariate analysis, the likelihood of returning to care was higher among US-born persons (RR 1.61 (95% CI: 1.29-2.01)) and significantly lower for persons whose last test occurred in earlier years (e.g., compared to 2011, 2010 RR 0.5 (95% CI: 0.41-0.62), 2009 RR 0.39 (95% CI:0.30-0.52), 2008 RR 0.22 (95% CI:0.15-0.32)).

Last Known CD4 Count for Persons with No Evidence of Care in 2012 but having ≥1 Test Reported 2006-2011



Conclusions: A substantial proportion of persons diagnosed 2006-2010 were out of care in 2012. One third had a CD4 count ≤350 at last test, yet few had evidence of re-engagement in 2013. Strategies to address attrition from care as well as re-engagement are needed. Persons with recent care may be particularly open to re-engagement efforts, suggesting the benefit of prompt action to return them to care.

1003 Care-Cascade Status of Partners of Persons With New HIV Infections in North Carolina

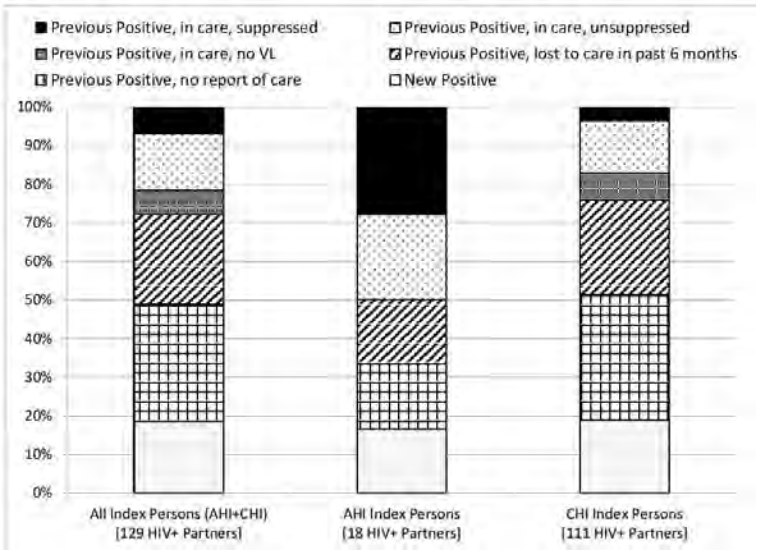
Anna B. Cope[1]; Lisa Hightow-Weidman[1]; JoAnn D. Kuruc[1]; Jenni Marmorino[1]; Steve Beagle[1]; Philip J. Peters[2]; Cynthia L. Gay[1]
[1]University of North Carolina, Chapel Hill, NC, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: HIV transmission risk is affected by HIV status awareness and care and treatment status. We aimed to describe the diagnosis, care, and viral suppression status of HIV-infected partners identified by persons newly diagnosed with HIV in North Carolina (NC).

Methods: The STOP study is a multi-site, prospective study assessing methods to detect acute HIV infection (AHI). In NC, participants (age >12 years) at 3 sexually transmitted infection clinics were screened for HIV infection from 9/2011 to 10/2013. For newly diagnosed persons (indexes), partner services interviews elicited information about past sex partners within a specified period (AHI indexes=3 months; chronic HIV infection [CHI] indexes=12 months). The HIV status (HIV-infected, HIV-uninfected, status-unknown) and diagnosis (new or previously diagnosed), care (CD4 or viral load [VL] reported in NC surveillance databases), and viral suppression (VL<50 copies/ml) status were determined for reported partners.

Results: Overall, 146 persons were newly diagnosed with HIV infection during the STOP study (20 AHI indexes; 126 CHI indexes). Index persons were predominately MSM (66%), young (median age 26 years), and black (86%). Index persons reported 791 sexual partners (80 by AHI indexes, 711 by CHI indexes). Over half of all partners were of unknown status (460 anonymous, 21 counselling-and-testing refusals, 45 testing-only refusals, 32 unlocatable). Of the remaining 331 partners, 129 (39%) were HIV-infected (24 newly diagnosed; 105 previously diagnosed). A total of 66 (63%) previously diagnosed partners had a reported VL/CD4 before the index diagnosis date; the last VL/CD4 for 30 (45%) of these partners was >6 months before the index diagnosis date, suggesting loss to care. Of those with a VL 6 months before the index diagnosis date (N=28), 19 were not virally suppressed (68%). AHI and CHI indexes reported a similar proportion of previously diagnosed partners; AHI indexes reported a higher proportion of virally suppressed, previously diagnosed partners (33% versus 4%; p=0.004). Half (N=80) of all indexes named ≥1 HIV-infected partner; 70 (48%) named ≥1 previously diagnosed partner.

Figure 1. Diagnosis, Care and Treatment Status of Named HIV-infected Partners, by Index Status: STOP Study, 2011-2013



Conclusions: Previously diagnosed partners, many of whom were not in care and virally suppressed, were prominent in networks of newly diagnosed persons. Prioritizing interventions to find previously diagnosed persons not in care and facilitate re-engagement and treatment could greatly impact HIV transmission.

1004 The Role of HIV Status Disclosure in Retention in Care and Viral-Load Suppression

Latesha E. Elopre; Andrew Westfall; Michael J. Mugavero; Anne Zinski; Greer Burkholder; Edward Hook; Nicholas Van Wagoner
University of Alabama at Birmingham, Birmingham, AL, US

Background: In the United States, retention in care is poor for patients infected with HIV and only 25% achieve viral load suppression. Knowledge that life expectancy and prevention of transmission to others is associated with adherence to anti-retroviral therapy suggests that better understanding of barriers to retention in care and effective viral load suppression is a priority. For newly diagnosed persons, the decision of whether and whom to disclose to is complex, with benefits weighed against perceived risks. The purpose of this study was to evaluate whether nondisclosure and selective disclosure of HIV status is associated with poor retention in HIV care and failure to achieve viral load suppression.

Methods: This retrospective analysis evaluated the relationship of disclosure to poor retention in care (a gap in care > 180 days) and sustained viremia (viral load > 200 copies/ml) measured at 12 months after initiating HIV care. Participants must never have previously received HIV care and be older than 19 years of age. Primary analyses included disclosure status treated dichotomously (no disclosure vs any disclosure). Secondary analyses then evaluated nondisclosure and selective disclosure (disclosure to family only, friends only, significant other only) compared to disclosure to 2 or more groups (referent). Univariate and multivariable (MV) logistic regression models were fit including factors known to be associated with disclosure and the study outcomes.

Results: From 2007-2013, 508 HIV infected patients presented to establish care, of whom 61% were African American, 53% had a CD4 + T lymphocyte count < 350 and 82% were men (60% men who have sex with other men). Of these, 65 (13%) reported nondisclosure and 258 (51%) reported selective disclosure. In primary MV analyses, nondisclosure was associated with poor retention in care (AOR 2.3; 95% CI 1.3, 4.1), but no relationship with sustained viremia was observed. In secondary MV analyses, the relationship between nondisclosure and poor retention in care was maintained (AOR 2.2; 95% CI 1.2, 4.3). Also, patients acknowledging selective disclosure to friends only (AOR 2.6; 95% CI 1.0, 6.5) or family only (AOR 2.9; 95% CI 1.2, 7.6) were more likely to have continuing viremia.

Conclusions: Evaluating disclosure patterns among patients establishing HIV care may help predict inconsistent care and lack of viral load suppression. Further work is needed to evaluate why this relationship exists and to guide future interventions to improve these HIV-outcomes.

1005 Alcohol and Substance Use and Timing of Presentation to HIV Care Across the United States

Jesse Abbott Klafter[1]; Daniel R. Drozd[3]; Michael J. Mugavero[2]; Katerina Christopoulos[4]; Christopher W. Mathews[7]; Joseph J. Eron[8]; Kenneth H. Mayer[6]; Matthew Mimiaga[5]; Mari Kitahata[3]; Heidi M. Crane[3]
Center for AIDS Research Network of Integrated Clinical Systems (CNICS)

[1]University of Washington, Seattle, WA, US; [2]University of Alabama at Birmingham, Birmingham, AL, US; [3]University of Washington, Seattle, WA, US; [4]University of California San Francisco, San Francisco, CA, US; [5]Harvard Medical School, Boston, MA, US; [6]Fenway Health, Boston, MA, US; [7]University of California San Diego (UCSD), San Diego, CA, US; [8]University of North Carolina, Chapel Hill, NC, US

Background: Alcohol and substance use are known to negatively impact multiple steps along the HIV care continuum including retention, adherence, and viral suppression. The association between alcohol and substance use and testing and linkage to care is less well characterized. CD4 count at care entry is a function of HIV testing timing and subsequent linkage to care. We examined the association between alcohol and substance use and CD4 count at HIV care entry.

Methods: Data from 6 CNICS sites from 2006-2013 were included. Patients complete a touch-screen-based assessment including alcohol and substance use measures as part of clinical visits. Patients were eligible for this study if they had no prior HIV care, were antiretroviral therapy naïve at the time of care entry, and had an assessment within 24 months of care entry (sensitivity analyses included 12 and 18 months). Our main outcomes were CD4 count as continuous and binary (<200) measures at care entry. We used linear and logistic regression to examine the association between these outcomes and alcohol and substance, adjusted for age, sex, race/ethnicity, depression, year of care entry, and site.

Results: 2025 patients were eligible. Any current drug use (a composite of current amphetamine, cocaine or opiate use) (20%) was associated with higher CD4 count at care entry (34 cells/mm^3 higher $p<0.05$) and lower likelihood of CD4<200 (OR 0.5 $p<0.01$) compared to those who never used drugs. In separate models, current intravenous (IV) drug use (5%) was associated with higher CD4 count (86 cells/mm^3 higher $p<0.01$) and lower likelihood of initial CD4<200 (OR = 0.4 $p<0.05$) compared to those who never used IV drugs. In a third set of models including separate amphetamine, cocaine and opiate use, current cocaine use was associated with lower likelihood of CD4<200 (OR 0.4 $p<0.01$). High risk alcohol use was not associated with CD4 count at care entry in any of our models, compared to non-drinkers. Findings were similar in sensitivity analyses.

Conclusions: Current substance use and IV drug use were associated with more timely presentation to HIV care as measured by initial CD4 count. This may reflect increased availability of HIV testing and linkage services among these patients or more frequent interactions with the health and/or criminal justice systems. These results have implications both for a universal test and treat strategies as well as for efforts to improve outcomes of HIV care among substance users.

1006 Marijuana Use and Its Nuanced Relationship With HIV Treatment Continuum Metrics

John A. Schneider[1]; Ethan Morgan[1]; Stuart Michaels[2]; Britt Skaathun[1]; Lindsay Young[1]; Robert W. Coombs[3]; Phil Schumm[1]; Dexter Voisin[1]; Sam Friedman[4]
UConnect Study Team

[1]University of Chicago, Chicago, IL, US; [2]NORC, Chicago, IL, US; [3]University of Washington, Seattle, WA, US; [4]National Development Research Institute, New York, NY, US

Background: Studies of relationships between drug use and HIV treatment have primarily focused on methamphetamine, cocaine or heroin use. Few studies, however, have focused on younger Black men who have sex with men (YBMSM) who have less drug use in aggregate when compared to other MSM, but likely have higher rates of marijuana use. We examine associations between marijuana use and key treatment continuum metrics in a population based sample of YBMSM in Chicago. Improving treatment continuum outcomes for YBMSM is critical to controlling the HIV epidemic domestically.

Methods: From 2013-2014 a representative sample of YBMSM 16-29 years old in Chicago (n=626) was generated using Respondent Driven Sampling (RDS). HIV antibody/Ag and RNA testing were performed from dried blood spots. RDS-weighted models examined associations between marijuana use (never, intermittent or daily), HIV testing, and downstream treatment continuum metrics. Models were adjusted for age, education, condomless sex, group sex, EtOH use, depression and other drug use.

Results: YBMSM had a 28% seropositivity rate; 31% of positives were virally suppressed. 32% of YBMSM reported using marijuana daily or multiple times daily, 27% never used and 41% reported intermittent use (weekly or less). MJ use was mildly correlated with ecstasy use ($r=0.15$; $p<0.001$) and popper use ($r= 0.11$; $p=0.008$), but not methamphetamine use ($r=0.07$; $p=0.09$)). In adjusted regression models, YBMSM who used marijuana were more likely to be HIV seropositive (aOR, 3.56; $p<0.05$) and HIV positive unaware (12.80, $p<0.001$). Among HIV seropositive individuals, compared to no use, intermittent but not daily marijuana use was associated with worse retention in HIV care (2 or more visits 3 months apart in previous year) (aOR, 6.10; $p=0.021$). Marijuana use was not associated with linkage to care, adherence to ARVs or viral suppression. Covariates in these models including alcohol and other drug use were also not associated with any of the continuum metrics.

Conclusions: Critical HIV treatment continuum components such as knowing one's status and retention in care are related to intermittent marijuana use. Specific marijuana use information should be collected from clients engaging in care that includes frequency of use which may help target HIV treatment interventions. A focus on drugs used by most affected populations such as YBMSM and their nuanced relationship with continuum metrics is warranted, particularly in the context of increasing social acceptability of marijuana.

1007 "Test-and-Treat" in the Netherlands

Ard van Sighem[1]; Luuk Gras[1]; Eline Op de Coul[2]; Daniela Bezemer[1]; Michiel van Agtmael[3]; Godelieve de Bree[4]; Peter Reiss[1]
On behalf of the ATHENA National Observational HIV Cohort

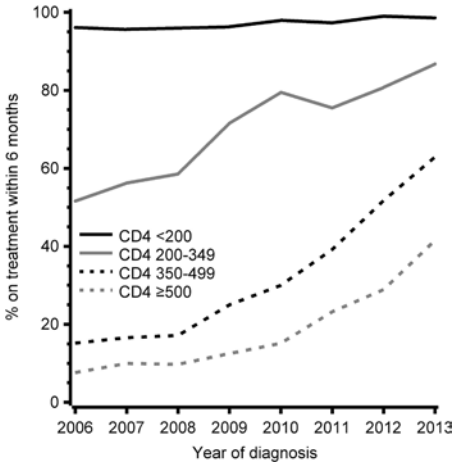
[1]Stichting HIV Monitoring, Amsterdam, Netherlands; [2]National Institute for Public Health and the Environment, Bilthoven, Netherlands; [3]VU University Medical Centre, Amsterdam, Netherlands; [4]Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands

Background: Early diagnosis and treatment of HIV, or 'test-and-treat', benefits individual patients and helps in preventing new infections. Treatment guidelines in the Netherlands now recommend starting combination antiretroviral treatment (cART) immediately, regardless of CD4 cell counts. We studied changes over time in the proportion of patients diagnosed with a recent infection and to what extent immediate treatment is adopted in clinical practice.

Methods: All HIV-1-infected patients diagnosed in 2006-2013, i.e., when information on recent infection was consistently collected for all patients, were selected from the ATHENA national observational HIV cohort. Patients were considered recently infected if in the 6 months before diagnosis they had a HIV-negative test, an indeterminate western blot, additional evidence of a known risk exposure, or symptoms of acute infection. CD4 count at diagnosis was the first pre-cART CD4 count ≤3 months after diagnosis.

Results: Of 9057 diagnosed patients, 1756 (19%) had evidence of recent infection: 1533 (87%) men who have sex with men (MSM), 124 (7%) men with other transmission route, and 99 (7%) women. Between 2006 and 2013, the proportion of recent infections increased from 21% to 31% in MSM ($p<0.001$), from 5% to 7% in women ($p=0.008$), and did not change in other men (7%; $p=0.4$). Recent infection was based on a previous negative test for 1188 (68%) patients, of whom 42% also had symptoms and 19% a known risk exposure. Overall, 884 (50%) patients had symptoms of acute infection. Median CD4 count was 500 (interquartile range, 364-680) cells/mm^3 and did not differ by risk group.

Of all 9057 patients, 86% had entered into care ≤6 weeks after diagnosis. Between 2006 and 2013, the proportion starting cART ≤6 months after diagnosis was >95% for those diagnosed with CD4 <200, increased from 52% to 87% for CD4 200-349, from 15% to 63% for CD4 350-499, and from 8% to 42% for CD4 ≥500 cells/mm^3 (see figure). The proportion on cART among patients diagnosed in 2013 did not differ by risk group. In patients with recent infection, the proportion on cART ≤6 months increased from 21% to 62%.



Conclusions: Almost one third of MSM is currently diagnosed with a recent infection, but in other groups, diagnosis of a recent infection remains uncommon. The proportion who started cART ≤6 months at high CD4 counts has rapidly increased in recent years, reflecting the adoption by both physicians and patients of changes in treatment guidelines.

1008 Estimates of HIV Prevalence, Proportion of Diagnosed Patients and Quality of Treatment in Switzerland

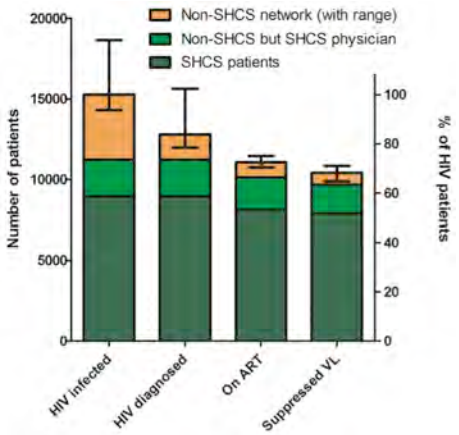
Philipp Kohler[2]; Axel J. Schmidt[3]; Bruno Ledergerber[2]; **Pietro L. Vernazza**[1]

[1]Cantonal Hospital St. Gallen, St. Gallen, Switzerland; [2]Universitätsspital Zürich, Zurich, Switzerland; [3]Federal Office of Public Health, Bern, Switzerland

Background: A recently published review article on the quality of HIV-care in the US showed that a considerable number of HIV infected individuals is either unaware of their diagnosis or not adequately treated. We aimed at conducting a similar analysis estimating the HIV prevalence, the proportion of diagnosed patients and the quality of HIV care in Switzerland.

Methods: Four levels of engagement in HIV-care were defined: a) HIV infected, b) HIV diagnosed, c) on antiretroviral treatment (ART), and d) with suppressed viral load (i.e. <200 RNA copies per ml). The Swiss HIV Cohort Study (SHCS) database was used to determine the proportion of treated SHCS patients including those with suppressed viral load. Furthermore, a survey among HIV care providers connected to the SHCS network was conducted regarding the proportion of treated non-SHCS patients (including those with suppressed viral load) within the SHCS network. The number of HIV-patients being treated outside the SHCS network was estimated based on ART sales data for Switzerland. Based on the total number of SHCS and non-SHCS patients being linked to care, we inferred the number of non-diagnosed HIV patients from a model reported by *Van Sighem et al. 2011* for MSM. For other transmission categories, a proportion of 25% undiagnosed individuals was assumed.

Results: In 2012, we estimate (a) 15,200 individuals infected with HIV living in Switzerland, corresponding to an overall prevalence of 0.19%. Of those, (b) 12,800 (84%) had been diagnosed. Based on sales data, adjusted for treatment change, adherence and PEP use, 11,100 patients (c) were receiving ART (87%), and 10,500 (d) had an undetectable viral load (95%). This results in an overall proportion of undetectable viral load of 69%. A vast majority of Swiss HIV patients (87%) was followed within the SHCS network, with an overall percentage of 70% registered in the SHCS.



Conclusions: The effectiveness of ART for patients within the SHCS network is high with a suppression rate of 95%. Interventions aiming at improving the current situation of HIV management in Switzerland will most likely have the greatest impact if applied to infected persons unaware of their diagnosis. Currently, one third of the HIV-infected population can serve as a source for onward transmission, half of which don't know their status.

1009 Medical Care Interruptions in HIV-infected Patients: Characteristics and Consequences

Lise Cuzin[1]; Pierre Dellamonica[2]; Yazdan Yazdanpanah[7]; Sabelline Bouchez[3]; David Rey[6]; Bruno Hoen[5]; André Cabié[4]

[1]Toulouse University Hospital, Toulouse, France; [2]University Hospital, Nice, Nice, France; [3]University Hospital, Nantes, France; [4]University Hospital, Fort de France, France; [5]University Hospital, Pointe à Pitre, France; [6]University Hospital, Strasbourg, France; [7]Hôpital Bichat-Claude Bernard, APHM, Paris, France

Background: To describe the consequences of medical care interruptions in a French cohort of HIV infected patients.

Methods: Retrospective study nested in the prospective Dat'AIDS cohort, which collects all medical and therapeutic information on HIV-infected patients in care in major University Hospitals in France.

Patients with at least 2 medical encounters between 01/2006 and 06/2013 were selected. Patients who had at least once a time interval between 2 visits >15 months were defined to have medical care interruption (MCI), as opposed to the remaining patients who had uninterrupted follow-up (UFU). Patients' characteristics at the time of HIV-diagnosis and at the censoring date were compared between groups. Cox proportional models taking interruptions as time dependant variables were built to assess the role of interruptions on survival (total and AIDS-free). Among the patients with at least one past interruption, characteristics and consequences were described.

Results: Among 11 116 patients, 824 had had at least one care interruption. They were younger at the time of HIV diagnosis (30 versus 33y, p<0.0001). Men having sex with men had a lower risk of care interruption by comparison with heterosexual patients (RR=0.81; 95%CI 0.69 - 0.96). Median MCI duration was 22 months (IQ25 18; 32), and the median CD4 loss during MCI - 169 cells (IQ25 -355; -69). A first AIDS defining event was reported in 91 patients after care resumption. In 53 cases this event was the very reason to come back to care (date of event less than one month after the resumption visit). At the censoring date, 52.2% of the patients with at least one care interruption had viral load below detection, versus 85.3% of the UFU, p<0.0001. MCI was an independent predictive factor of AIDS (RR=2.54; 95%CI 2.10 - 3.09) and death (RR=2.65; 95%CI 1.94 - 3.61).

Conclusions: MCI was related with pts overall and AIDS-free survival, and with the proportion of viral loads below detection in our cohort, compromising individual and collective treatment benefits.

1010 Blood Donor Test-Seeking Motivation and Prior HIV Testing Experiences in São Paulo

Hong-Ha M. Truong[1]; Paula Blatyta[2]; Sandra Montebello[2]; Sandra Esposti[2]; Fatima Hangai[2]; Nanci Salles[2]; Alfredo Mendrone[2]; Ester C. Sabino[3]; Willi McFarland[4]; Thelma T. Gonçalez[5]

[1]University of California San Francisco, San Francisco, CA, US; [2]Fundação Pró-Sangue/Hemocentro de São Paulo, São Paulo, Brazil; [3]University of São Paulo, São Paulo, Brazil; [4]San Francisco Department of Public Health, San Francisco, CA, US; [5]Blood Systems Research Institute/University of California San Francisco, San Francisco, CA, US

Background: Blood banks in many countries are working towards universal testing of all donations and are equipped to perform a high volume of HIV tests. However, use of the blood donation process for the purpose of diagnosing HIV among persons at risk is at odds with the mandate to keep the blood supply free of HIV contamination and to provide proper counseling for those at risk. Nevertheless, HIV test-seeking behavior among donors has been observed worldwide and may pose a threat to the safety of the blood supply. We evaluated current testing-seeking motivations and prior alternative HIV testing experiences among blood donors in São Paulo.

Methods: All candidate donors presenting between August 2012 and May 2013 at Fundação Pró-Sangue Hemocentro, the largest blood bank in Brazil, were consecutively approached, screened for donor eligibility and recruited. Questionnaires were administered through audio computer-assisted self-interview.

Results: Among 11,867 donors, 38% previously tested for HIV apart from blood donation, of whom 47.7% tested at public facilities and 2.7% acknowledged getting tested for HIV as the primary reason for donating. Fifty-five percent of donors had not heard of alternative public testing sites. Lack of awareness of alternative testing sites was significantly associated with test-seeking behavior (p<0.001). Dissatisfaction with a prior alternative testing experience was reported by 2.5% of donors. Current test-seeking motivation was associated with dissatisfaction with a prior alternative testing experience (p=0.004), testing at a public alternative facility (p<0.001) and hepatitis C (HCV) infection (p<0.001). The most common reasons for dissatisfaction were too long a wait to get tested and for results, counseling was too long, lack of privacy and low confidence in the equipment and accuracy of test.

Conclusions: Lack of awareness of the availability of free and confidential public HIV testing services and dissatisfaction with past HIV testing and counseling experiences motivate some individuals to test at blood banks. This test-seeking behavior may compromise the safety of the blood supply if donors at elevated risk for HIV donate during the window period. Such donors may also have elevated risk for other transfusion-transmissible infections such as HBV, HCV and syphilis. Test-seeking behavior among blood donors may be best addressed by improving alternative testing programs, particularly with respect to decreasing time delays, increasing privacy and enhancing test accuracy.

TUESDAY, FEBRUARY 24, 2015

Session P-W2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HIV Testing and the Continuum of Care in the Developing World

1011 Treatment Interruptions in ART Programmes in Resource-Limited Settings: 2003 to 2013

Gail B. Cross[1]; Tim Spelman[2]; Daniel P. O'Brien[4]; Nathan Ford[3]; Jane Greig[4]; James H. McMahon[1]

[1]Monash University/Alfred Hospital, Prahan, Australia; [2]Burnet Institute, Melbourne, Australia; [3]World Health Organization (WHO), Geneva, Switzerland; [4]Médecins Sans Frontières, London, United Kingdom

Background: Antiretroviral therapy (ART) treatment interruptions (TI), are associated with increased risk of mortality, opportunistic infections, virological failure and drug resistance. This study describes the frequency and risk factors for TI in Médecins Sans Frontières (MSF) ART programmes in 33 sites across Asia and Africa.

Methods: Analysis of routinely collected data from ART programs in 11 countries across Asia and Africa between 2003 and 2013. Included variables were: gender, age, marital status, region (Asia or Africa), CD4 count and WHO stage at ART initiation. TI was defined as a ≥ 90 day unstructured break from ART calculated from the last day the previous ART prescription would have run out until the date of the next ART prescription. Factors predicting TI were assessed in unadjusted and adjusted cox proportional hazards regression with a conditional risk-set to account for repeated events. Tests for interaction were performed in adjusted models.

Results: 40632 patients were included from 11 countries across 33 sites (17 Africa, 16 Asia). Median duration of follow-up was 1.61 years (IQR: 0.54-3.31 years) and 3386 (8.3%) patients died. There were 14817 TIs of ≥ 90 days with 10162 (25%) patients having more than one TI. In the adjusted model males were at lower risk of a TI compared with female patients (aHR: 0.94, p=0.003), and age of 20-59 appeared to be protective (20-39 years aHR 0.87, p=0.004; 40-59 years aHR 0.86, p=0.005) as compared to those < 20 years of age (Table). Preserved immune function, CD4 T-cell count 200-350 or > 350, were protective of TI as compared to CD4 < 200 (CD4 200-350 aHR 0.89, p<0.001; CD4 > 350 aHR 0.87, p=0.006). In addition more advanced clinical disease (WHO stage 3 aHR 1.10, p=0.009; stage 4 aHR of 1.21, p < 0.001) was also predictive of increased risk of TI in the same adjusted model. Marital status was not protective of TI while people from Asian countries were less likely to experience a TI when compared with those from African nations (aHR: 0.82, p< 0.001).

Unadjusted and Adjusted Predictors of Treatment Interruption

Predictor	Level	Unadjusted Hazard Ratio (95% CI)	p-value	Adjusted Hazard Ratio (95% CI)	p-value
Sex	Female	Ref.		Ref.	
	Male	0.94 (0.90-0.98)	0.003	0.94 (0.90-0.98)	0.003
Age	<20	Ref.		Ref.	
	20-39	0.81 (0.74-0.89)	<0.001	0.87 (0.79-0.96)	0.004
	40-59	0.79 (0.71-0.87)	<0.001	0.86 (0.78-0.96)	0.005
	60+	0.86 (0.67-1.11)	0.259	1.07 (0.82-1.39)	0.607
WHO stage at ART initiation	1	Ref.		Ref.	
	2	1.07 (0.98-1.17)	0.151	1.03 (0.95-1.13)	0.469
	3	1.12 (1.05-1.21)	0.001	1.10 (1.02-1.18)	0.009
	4	1.23 (1.14-1.33)	<0.001	1.21 (1.12-1.30)	<0.001
CD4 count at ART initiation	<200	Ref.		Ref.	
	200-350	0.87 (0.82-0.93)	<0.001	0.89 (0.83-0.95)	<0.001
	>350	0.86 (0.78-0.95)	0.003	0.87 (0.78-0.96)	0.006
Marital status	Not married	Ref.		Ref.	
	Married	0.97 (0.93-1.01)	0.178	1.02 (0.97-1.06)	0.479
Region	Africa	Ref.		Ref.	
	Asia	0.79 (0.75-0.83)	<0.001	0.82 (0.78-0.87)	<0.001

Conclusions: TIs were frequent in patients in ART programs in LMICs and associated with younger age, female gender and more advanced HIV. Further evaluation of predictors of TI and interventions to reduce their occurrence are warranted in all LMICs.

1012 Time to ART Qualification and Retention Among Patients With Early HIV in Haiti

Rita T. Dadaille[1]; Serena P. Koenig[1]; Kelley Henessey[2]; Ellie Cooper[2]; Pierre Cremieux[2]; William J. Pape[1]
Analysis Group; Les Centres GHESKIO IT Team

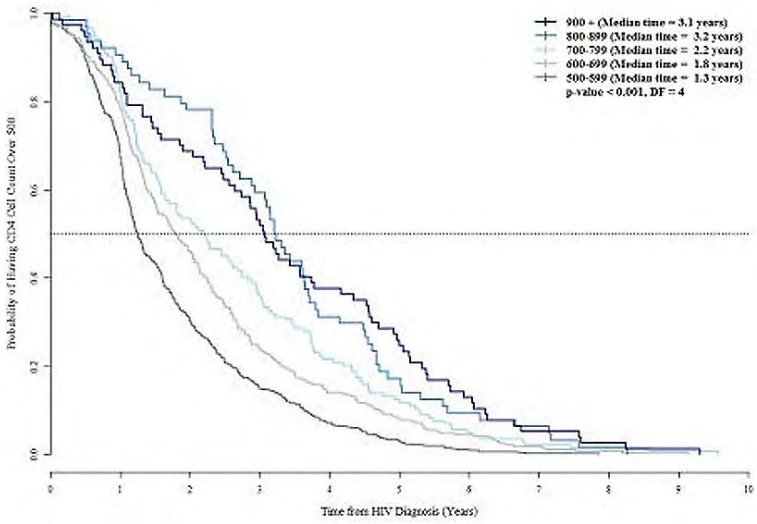
[1]*Gheskio Centers, Port au Prince, Haiti;* [2]*Analysis Group, Boston, MA, US*

Background: Attrition is high from HIV testing to antiretroviral therapy (ART) initiation, particularly among patients who do not yet qualify for ART. We evaluated pre-ART outcomes for patients with early HIV over the last decade at the GHESKIO Center in Port-au-Prince, Haiti.

Methods: We included all adult patients (age ≥18 years) who tested positive for HIV from March 2003 through February 2012. We calculated retention from HIV testing to ART initiation, with 2 years of pre-ART follow-up. In addition, among patients with CD4 >500 cells/mm^3, we conducted multivariate analyses to evaluate predictors of patient retention, and analyzed the time to CD4 cell count ≤500 cells/mm^3.

Results: A total of 22,317 patients received positive HIV test results; 13,574 (61%)were female, with median age of 35 years. Of patients who tested HIV-positive, 14,398 (65%) had blood drawn for CD4 count, an increase of 56% from year 1 (48%) to year 9 (75%). Overall, 13,047 (91%) returned for results and3,061 patients (89%) had CD4 count >500 cells/mm^3. Among patients with CD4 count >500 cells/mm^3, 1,591 (46%) were retained in pre-ART care for ≥2 years or initiated ART. Predictors of retention included later year of HIV testing (OR 1.04; 95% CI: 1.01-1.08), education (primary vs. none: OR 1.48; 95% CI: 1.23-1.77), female gender (OR 1.46; 95% CI: 1.23-1.74), relationship status (stable partnership vs. single: OR 1.41; 95% CI: 1.16-1.71), residence zone in Port-au-Prince (OR 1.39; 95% CI: 1.04-1.85), and TB after enrollment (OR 3.44; 95% CI: 2.29-5.18). The median time to CD4 count ≤500 cells/mm3 was 19.9 months (see Figure 1).

Figure 1. Kaplan-Meier Curve for the Probability of Reaching CD4 Cell Count 500 Stratified by Initial CD4 Cell Count (cells/mm^3) in Patients Reaching CD4 Count 500



Conclusions: Though retention in care for patients with early HIV disease is slowly improving over time, <50% have been retained in care over the past decade. The median time for CD4 count decline to ≤500 cells/mm^3 is 19.9 months. Further studies on the impact of ART on retention in care for patients with early HIV are urgently needed.

1013 Awareness of HIV Diagnosis in the Swaziland HIV Incidence Measurement Survey

Tanya M. Ellman[1]; Ruth Emerson[4]; Deborah Donnell[4]; Neena M. Philip[1]; Rejoice Nkambule[2]; Naomi Bock[3]; Peter Ehrenkranz[5]; George Bicego[3]; Jessica E. Justman[1]

[1]ICAP at Columbia University, New York, NY, US; [2]Ministry of Health, Mbabane, Swaziland; [3]US Centers for Disease Control and Prevention, Atlanta, GA, US; [4]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [5]Centers for Disease Control and Prevention, Mbabane, Swaziland

Background: Awareness of HIV diagnosis at the population level may be a useful way to gauge effectiveness of testing programs. In a 2007 household-based national survey, 31% of adults aged 15-49 were HIV-infected, and of these, 55% reported no prior HIV testing and were therefore unaware of their diagnosis. We report on the prevalence of undiagnosed HIV among HIV-infected adults in Swaziland in 2011.

Methods: In the Swaziland HIV Incidence Measurement Survey (SHIMS), a nationally representative sample of 18,172 men and women aged 18-49, completed household-based counseling and rapid HIV testing and provided clinical and demographic information, including self-reported results of prior HIV tests. Seropositive individuals who reported a prior positive test were defined as aware of their diagnosis; seropositive individuals who reported no prior HIV testing or a prior negative, unknown or indeterminate test, were defined as unaware. Data were weighted to adjust for sampling methods and differences in non-response to achieve population representativeness. Characteristics of those aware and unaware were compared using logistic regression models.

Results: 5,829 (32%) adults tested HIV-seropositive in SHIMS, and of these 2,238 (38%) were unaware of their diagnosis. Undiagnosed HIV was more common among men than women (50% vs 32%, p <0.001) and among younger adults, 18-29 y, than older adults, 40-49 y (46% vs 31%, p <0.001); neither current pregnancy nor circumcision status correlated with awareness. Adjusting for marital status, education background, and current employment, men were more than twice as likely to be unaware of their HIV diagnosis compared to women (aOR 2.54, 95% CI 2.25, 2.87) and younger adults more than twice as likely as older adults to be unaware (aOR 2.44, 95% CI 2.04, 2.86). Among all seropositive individuals, 960 of 5829 (16.5%) reported no prior HIV testing. Among those unaware of their diagnosis, 576 of 2238 (26%) reported a negative HIV test in the year prior to SHIMS.

Conclusions: While over one-third of HIV-infected adults in Swaziland were unaware of their diagnosis, only one-sixth reported no prior testing, reflecting considerable testing uptake since 2007, when more than half reported this. Men and younger individuals should be targeted for testing in the community, opportunities for testing during contact with the health care system should not be missed, and annual testing of all adults in high prevalence countries should be considered.

1014 Who Is at Risk of Being Untested and Unaware of HIV-Positive Status in KwaZulu-Natal?

Helena Huerga[1]; Gilles Van Cutsem[2]; Jihane Ben Farhat[1]; Malika Bouhenia[1]; Matthew Reid[2]; David Maman[1]; Jean-François Etard[1]; Thomas Ellman[2]

[1]Epicentre, Paris, France; [2]Médecins Sans Frontières, Cape Town, South Africa

Background: HIV prevalence in KwaZulu-Natal (KZN) is one of the highest in the world. HIV testing and positive status awareness are key aspects in the control of the epidemic. We assessed HIV testing and positive status awareness rates as well as associated factors in Mbongolwane and Eshowe, KZN, South Africa.

Methods: Cross-sectional population-based survey. A cluster sampling and geospatial random selection was used to identify households visited. Individuals aged 15-59 years living in the area were eligible. Face-to-face interviews were carried out followed by rapid HIV testing on site and blood collection for other HIV related tests.

Results: In total, 5649 (84.5%) of 6688 eligible individuals were included: 62.3% women and 37.7% men. Overall HIV prevalence was 25.2% (95%CI: 23.6-26.9): 30.9% in women and 15.9% in men. Among all individuals, 4598 (81.4%, 95%CI: 79.8-82.9) declared to ever having had an HIV test prior to the survey (88.4% of women vs 69.8% of men, p<0.001). In total, 25.6% (95%CI: 23.4-27.9) of participants aged 15-19 years and 30.0% (95%CI: 27.7-32.5) of men less than 30 years had never tested. Participants had been tested a median of 3 times (IQR: 2-4) and 48.2% had their last test done in the previous 6 months. A majority, 78.6%, were tested in the public sector, 18.9% by MSF and 2.5% by others. In total, 1065 of 1416 HIV positive participants, 75.2% (95%CI: 72.9-77.4), were aware of their HIV positive status. Of HIV positive participants aged 20-24 years, 47.2% (95%CI: 40.2-54.3) overall and 83.3% of men were unaware of their status. In multivariate analyses, young people (<35 years), men and those with more than one sexual partner in the 12 months prior to the survey, were more at risk of being untested for HIV and unaware of their HIV infection (table). In addition, individuals over 45 years were less likely to have tested for HIV and those never married less likely to be aware of their positive status.

	Untested for HIV			Unaware of HIV positive status		
	Adjusted OR	95%CI	p	Adjusted OR	95%CI	p
Age group						
35-44	1			1		
15-24	2.3	1.7-3.2	<0.001	5.7	3.5-9.2	<0.001
25-34	1.7	1.2-2.4		2.8	1.9-4.2	
45-59	2.1	1.4-3.0		1.3	0.8-2.1	
Gender						
Women	1			1		
Men	4.4	3.7-5.3	<0.001	1.8	1.3-2.6	<0.001
Marital status						
Married/Living together	1			1		
Never married	1.0	0.7-1.3	0.19	1.6	1.1-2.3	0.07
Divorced/Separated/Widowed	0.6	0.4-1.1		1.3	0.6-1.3	
Number of sexual partners						
1	1			1		
>1	1.3	1.0-1.7	<0.001	2.2	1.4-3.3	<0.001
0	2.7	2.2-3.3		1.0	0.7-1.4	

Factors associated with not being tested for HIV and not being aware of HIV positive status

Conclusions: HIV testing and positive status awareness are high in KwaZulu-Natal. However, a considerable proportion of young men were not tested and the majority of positive men aged 20-24 years were not aware of their status. Youth, men and people with more than one sexual partner are groups at risk of not being tested for HIV and not aware of their HIV status. HIV testing strategies should target these groups in order to improve their access to treatment and more effectively control the epidemic.

1015 Impact of Unplanned Care Interruption on Immune Recovery After ART Initiation in Nigeria

Aimalohi A. Ahonkhai[1]; Juliet Adeola[2]; Bolanle Banigbe[2]; Ifeyinwa Onwuatuelo[2]; Ingrid V. Bassett[1]; Elena Losina[3]; Kenneth A. Freedberg[1]; Prosper Okonkwo[2]; Susan Regan[1]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [2]AIDS Prevention Initiative Nigeria, Jabi District, Nigeria; [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US

Background: Unplanned care interruption (UCI) from HIV treatment is common in most settings. The clinical impact of UCI has not been well studied in resource-limited settings. Our objective was to determine the immunologic consequence of UCI in the first year on antiretroviral therapy (ART) in Nigeria.

Methods: We examined data on adults (≥15 years) who enrolled in HIV care and started ART at a university-affiliated HIV clinic between 1/2009 and 12/2011. Follow-up was through 12/2012. In this retrospective cohort analysis, UCI was defined as ≥90 days with no clinician, laboratory, or pharmacy visits, but later return to care. We categorized patients into 3 groups: 0, 1, or ≥2 UCI in the first year on ART. We used multivariate repeated measures linear regression with patient as a random effect. We modeled the change in CD4 count early (1-6 months) and later (7-12 months) after ART initiation in each group, and determined the impact of UCI on predicted CD4. The model was adjusted for CD4 count and tuberculosis diagnosis at ART initiation in addition to patient age and sex.

Results: Among the 2,029 patients in our cohort 69% were female, and median age was 32 years [IQR 27, 39], and 4% had tuberculosis co-infection at enrollment. Fifty-four percent of patients had 0, 37% had 1, and 8% had ≥2 UCI. Follow-up CD4 was not available for 380 patients within one year of observation. Of the remaining 1,649 patients, mean baseline CD4 cell counts for those with 0, 1, and ≥2 UCI were 228/uL [SD 176], 354/uL [SD 228], and 392/ul [SD 241]. Overall, mean CD4 increase was 11 cells/uL/month [95%CI 8-14] in months 1-6, and 4 cells/uL/month [95%CI 2-5] in months 7-12. Patients with 1 UCI gained an average of 52 cells/ul [95% CI 35-68] fewer than those with 0 UCI. Those with ≥2 UCI lost 172 cells/uL at one year, ending with substantially lower counts (228/uL, 95%CI 184-271) than 0 UCI (327/uL, 95%CI 320-334), despite starting with much higher counts.

Conclusions: UCI was extremely common and occurred in almost half of the patients in a cohort initiating ART in Nigeria. UCI was associated with blunted CD4 cell responses in the first year on ART. Despite initiating ART with the highest counts, CD4 losses were greatest in patients with ≥2 UCI, negating the potential benefit of earlier care. Interventions to prevent interruptions in HIV care are critical to ensure the maximal benefits of ART.

1016 Linkage to HIV Care Among Men Who Have Sex With Men and Drug Users in India: Getting to 90

Sunil S. Solomon[1]; Allison M. McFall[2]; Aylur K. Srikrishnan[3]; Gregory M. Lucas[1]; Canjeeveram K. Vasudevan[3]; David D. Celentano[2]; Muniratnam S. Kumar[3]; Suniti Solomon[3]; Shruti H. Mehta[2]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]YR Gaitonde Centre for AIDS Research and Education, Chennai, India

Background: UNAIDS has set an ambitious target of 90/90/90 by 2020. While the first 90 assumes 90% of those infected will be aware of their status, the second 90 assumes 90% of those diagnosed are linked to care and initiated on ART. This can be particularly challenging among key populations (men who have sex with men [MSM] and people who inject drugs [PWID]) in resource-limited settings (RLS). Identifying modifiable factors associated with linkage to care in these groups will be critical to achieving this target.

Methods: 26,503 individuals (MSM=12,022 and PWID=14,481) were recruited across 27 sites in India (~1000/site) using respondent-driven sampling. Participants had to be ≥18 years and self-identify as male and report sex with a man in the prior year (MSM) or injection drug use in the prior 2 years (PWID). 1726 of the 4051 (41%) HIV positive-persons were aware of their status and included. Linkage was defined as ever having visited a health care professional for HIV after diagnosis. We explored whether there were modifiable factors around the time of diagnosis that discriminated between those linked and not linked using multi-level logistic regression and receiver operating characteristic curves (AUC).

Results: Median age was 35; 64% of PWID were male. Overall, 80% were linked to care. Among those not linked, 59% had been diagnosed in the past year, 20% 1-2 years ago and 21% >2 years ago. The primary reasons for not seeking care were not being ready/interested (51%) and not knowing where to go (10%). Modifiable factors that best discriminated those who were and were not linked included receiving tangible help with a medical referral at the time of diagnosis such as an appointment/transportation (odds ratio [OR]: 9.2, 95% confidence interval [CI]): 5.2-16.5) and disclosure of HIV status to ≥1 person at diagnosis (OR: 2.7; 95% CI: 1.5, 4.8). The AUC for these two factors was 0.85 (Figure 1), which was significantly higher than the AUC for demographics (0.79) or other combinations of modifiable factors. Overall, 91% of those who responded positively to both of these questions were linked vs. only 41% of those who responded no to both.

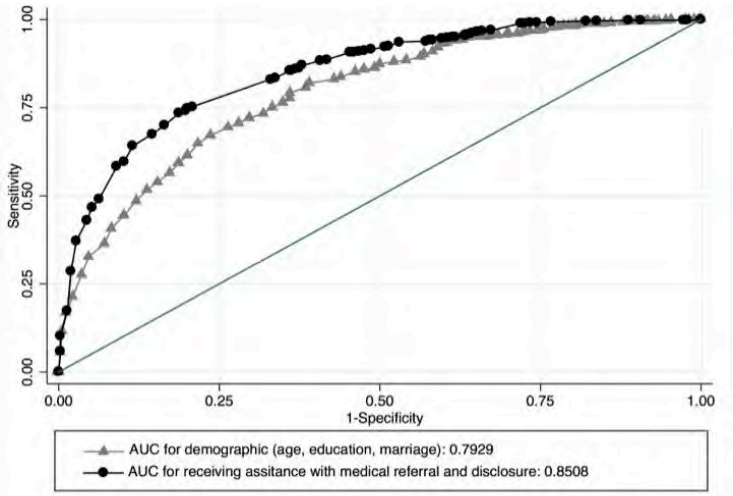


Figure 1. Area under the ROC curve (AUC) for demographic and modifiable factors

Conclusions: We identified two simple modifiable factors that could substantially impact linkage to care among MSM and PWID in RLS. Promoting tangible assistance with referral and disclosure at diagnosis are simple easy to implement strategies even in the context of community or home-based testing that could help achieve UNAIDS targets.

WEDNESDAY, FEBRUARY 25, 2015

Session P-W3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Risk Factors for Transmission in MSM

1017 Sex Pro: A Personalized HIV Risk Assessment Tool for Men Who Have Sex With Men

Hyman Scott[1]; Eric Vittinghoff[2]; Risha Irving[3]; Albert Liu[1]; Sheldon D. Fields[5]; Manya Magnus[6]; Darrell P. Wheeler[7]; Kenneth H. Mayer[4]; Beryl A. Koblin[8]; Susan P. Buchbinder[1]

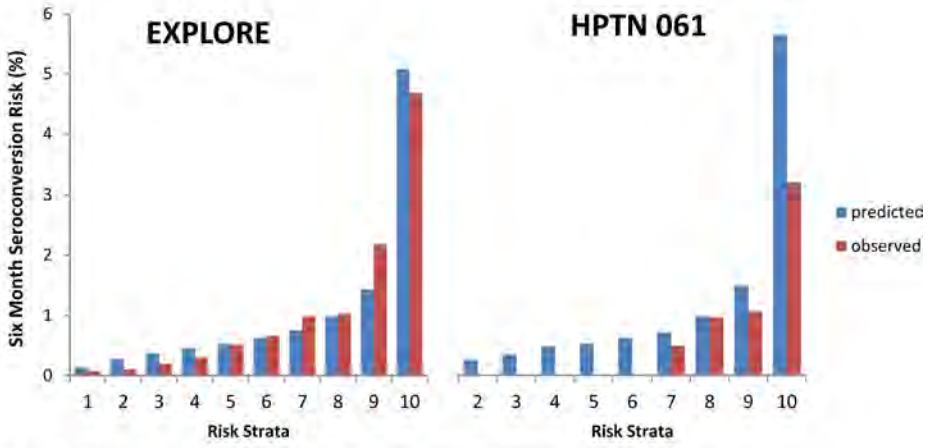
[1]San Francisco Department of Public Health, San Francisco, CA, US; [2]University of California San Francisco, San Francisco, CA, US; [3]Johns Hopkins University School of Medicine, Baltimore, MD, US; [4]Fenway Health, Boston, MA, US; [5]Florida International University, Miami, FL, US; [6]George Washington University, Washington, DC, US; [7]Loyola University Chicago, Chicago, IL, US; [8]New York Blood Center, New York, NY, US

Background: Personalized risk assessments can assist individuals and providers in determining who may most benefit from HIV prevention interventions, such as Pre-exposure Prophylaxis (PrEP). We developed an HIV risk assessment tool for men who have sex with men (MSM) and sought to validate it among a modern cohort of Black MSM, the group with the highest HIV incidence in the US.

Methods: Two efficacy trials of MSM in the US from 1998 through 2003, (VAX004 vaccine trial and EXPLORE behavioral trial) were used to develop and validate the risk model. The HIV Prevention Trials Network (HPTN) 061, which enrolled Black MSM from 2009-2010, was used as a contemporary validation cohort. Self-reported sexual risk behavioral data by partner serostatus, updated at six month visits, included non-condom receptive anal intercourse (ncRAI), non-condom insertive anal intercourse (ncIAI), and receptive anal intercourse with a condom (cRAI). Other self-reported risk factors included numbers of HIV-negative anal sex partners, drug and heavy alcohol use, and sexually transmitted infections (STIs). A total of 561 HIV seroconversions were identified among 8,950 participants in EXPLORE and VAX004. The final model includes age (<35, ≥35), race/ethnicity, numbers of ncRAI, ncIAI, and cRAI contacts, numbers of HIV-negative anal sex partners, having 1 HIV-negative partner only, and indicators for heavy alcohol use, methamphetamine and poppers, and self-report of STIs.

Results: There were 28 HIV seroconversions among 1,164 initially HIV-negative Black MSM in HPTN 061 who were eligible for follow-up. The cross-validated C-statistic in the development cohort, EXPLORE, was 79.5, while external validation C-statistics were 73.7 in VAX004 and 73.2 in HPTN 061, reflecting good model fit. All 28 seroconversions in HPTN 061 occurred among men in the top four deciles of risk predicted by the model (Figure). Model variables of age <35 (OR=4.69; 95%CI 1.89-11.6), heavy alcohol use (OR=4.34; 95%CI 1.95-9.65), and reporting an STI (OR=4.62; 95%CI 1.56-13.7) were associated with incident HIV infection in HPTN 061.

Figure: Validation of a personalized HIV risk model in EXPLORE and HIV Prevention Trials Network (HPTN) 061.*



*Cross-validation in EXPLORE and external validation in HPTN 061.

Conclusions: We developed and validated a risk assessment model for MSM which can be used to provide individualized feedback on HIV risk. The model retained good ability to distinguish levels of HIV risk in a recent cohort of Black MSM, and may be useful for improving awareness of HIV risk among MSM, risk stratification by providers, and uptake of HIV prevention interventions including PrEP.

1018 Unreported Sexual Risk Behavior Among MSM Newly Diagnosed With HIV Infection

Hsiu Wu[1]; Lisa B. Hightow-Weidman[2]; Cindy L. Gay[2]; Tonyka Jackson[3]; Emily Pike[2]; Jenni Marmorino[2]; Steve Beagle[2]; Laura Hall[3]; Philip J. Peters[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]University of North Carolina, Chapel Hill, NC, US; [3]ICF International, Atlanta, GA, US

Background: HIV prevention interventions such as acute HIV infection screening and pre-exposure prophylaxis (PrEP) are targeted to men who have sex with men (MSM) who self-report high-risk behavior. In this study, we described the characteristics of a sample of MSM in North Carolina, newly diagnosed with HIV infection, and assessed their self-reporting of HIV risk behaviors.

Methods: The STOP study is a multi-site, prospective study evaluating methods to detect acute HIV infection. In North Carolina, participants (age > 12 years) at three sexually transmitted infection clinics were asked about HIV-related risk behaviors when screened for HIV infection. Participants diagnosed with HIV infection then received partner services and were interviewed to elicit contact information for their sex partners. HIV tests were provided to partners with unknown HIV status. We compared risk behaviors reported before testing and during partner services interviews and described factors associated with discordant responses among MSM who tested positive for HIV infection.

Results: Among 16,892 male participants who received HIV testing from September 2011 to October 2013 in North Carolina, 179 (1.1%) were diagnosed with HIV infection of whom, 145 (81.0%) received partner services. Of 113 HIV-infected men (median age of 24 years, 85.0% black) who reported having male sex partners during partner services

interviews, 26 (23.0%) did not report male sex partners at the time of HIV testing (Table). Compared with MSM who reported male sex partners at the time of testing, those who did not had a similar number of male sex partners (median 3 vs. 4 male sex partners, p=0.41) but were more likely to have at least one female sex partner (30.8% vs. 6.9%, p=0.001). A similar proportion of MSM who did not report male sex partners at the time of testing had at least one HIV-infected partner compared with MSM who did report sex partners at the time of testing (82.4% vs. 81.2%, p=1.00).

Table. Characteristics of men who have sex with men (MSM) stratified by whether they reported male sex partners at the time of HIV testing, September 2011 - October 2013, North Carolina

	MSM who reported male sex partners at testing (n=87)	MSM who did not report male sex partners at testing (n=26)	*p*-value
Median age, years (IQR)	24 (22—30)	23.5 (20-28)	0.37
Race/Ethnicity, n (%) White Black/African American Other	13 (14.9) 73 (83.9) 1 (1.2)	3 (11.5) 23 (88.5) 0 (0)	0.77
HIV final status, n (%) Established HIV infection Acute HIV infection	76 (87.4) 11 (12.6)	24 (92.3) 2 (7.7)	0.73
Median number of reported male sex partners in past 12 months, n (IQR)	4 (2—6)	3 (2—5)	0.41
Reporting sex with an HIV positive partner at the time of testing, n (%) Yes No	23 (26.4) 64 (73.6)	0 (0.0) 26 (100.0)	0.002
Reported at least one female sex partner in past 12 months, n (%) Yes No	6 (6.9) 81 (93.1)	8 (30.8) 18 (69.2)	0.001
Named at least one sex partner in partner services, n (%) Yes No	69 (79.3) 18 (20.7)	17 (66.7) 9 (33.3)	0.14
Had ≥1 named sex partners confirmed with HIV infection in partner services*, n (%) Yes No	56 (81.2) 13 (18.8)	14 (82.4) 3 (17.7)	1.00

* Among those named at least one sex partner in partner services

Conclusions: A significant proportion of MSM newly diagnosed with HIV infection did not report accurate risk behavior information at the time of HIV testing. To customize HIV prevention interventions in disproportionately affected populations such as young black MSM, novel strategies are needed to accurately assess risk in these populations.

1019LB HIV Transmission in Male Serodiscordant Couples in Australia, Thailand and Brazil

Andrew E. Grulich[1]; Benjamin R. Bavinton[1]; Fengyi Jin[1]; Garrett Prestage[1]; Iryna B. Zablotska[1]; Beatriz Grinsztejn[2]; Nittaya Phanuphak[3]; Richard Moore[4]; Kersten K. Koelsch[1]
On behalf of the Opposites Attract Study Group

[1]University of New South Wales, Sydney, Australia; [2]Instituto de Pesquisa Clínica Evandro Chagas, Rio de Janiero, Brazil; [3]Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [4]Northside Clinic, Melbourne, Australia

Background: Numerous prospective studies have demonstrated that HIV transmission is greatly reduced in heterosexual HIV serodiscordant couples when the HIV-positive partner (HPP) is receiving combination anti-retroviral therapy (cART) with undetectable viral load (UVL). Comparable data in homosexual male serodiscordant couples (HM-SDC) are extremely limited. We report a pre-specified interim analysis of the relationship between UVL and HIV transmission in the Opposites Attract observational cohort study of HM-SDC in Australia, Bangkok and Rio de Janeiro.

Methods: HM-SDC reporting regular anal intercourse with each other were recruited through clinical sites. Detailed information on sexual risk behaviours was collected at each visit from the HIV-negative partner (HNP). HNPs were tested at baseline and follow-up for HIV antibodies and STIs (sexually transmitted infections), and HPPs for HIV viral load and STIs. Incidence rates were calculated per couple-year of follow-up (CYFU) using person-year methods, and stratified by whether different forms of condomless anal intercourse (CLAI) were reported. UVL was defined as <200 copies/mL. One-sided confidence intervals (CI) were calculated using the exact Poisson method. Linked HIV transmission in couples was defined by phylogenetic analysis.

Results: By December 2014, 234 HM-SDC were enrolled: 135 from Australia, 52 from Bangkok and 47 from Rio de Janeiro. There were a total of 150.0 CYFU in 152 couples with at least one follow-up visit of whom 65 (42.8%) were in a non-monogamous relationship. At baseline, 84.2% of HPPs were on cART and in total 82.9% had UVL. STI prevalence was 11.2% in HPPs and 6.6% in HNPs. There were 90.8 CYFU in periods where CLAI was reported with a total of 5,905 acts of CLAI in 88 couples. There were no linked HIV transmissions. The upper limit of the 95% CI of the transmission rate was 4.06/100 CYFU for periods in which CLAI was reported, and 6.46/100 CYFU for periods in which receptive CLAI was reported.

	Linked transmissions (n)	Couple-years of follow up (CYFU)	No. of CLAI acts	Incidence rate per 100 CYFU (95% CI)
Overall	0	149.96	5905	0 (0-2.46)
Any CLAI	0	90.83	5905	0 (0-4.06)
Insertive CLAI	0	77.87	3569	0 (0-4.74)
Receptive CLAI	0	57.08	2337	0 (0-6.46)
Any CLAI when VL <200 copies	0	88.59	5656	0 (0-4.16)
Any CLAI when VL >200 copies	0	2.00	237	0 (0-184)

HIV incidence by category of condomless anal intercourse reported

Conclusions: There were no linked HIV transmissions in 150 CYFU in these HM-SDC, despite close to 6,000 acts of CLAI. The upper confidence limit of the transmission rate during follow-up in periods during which CLAI was occurring was 4.06/100 CYFU. These data add to emerging evidence that the rate of HIV transmission in HM-SDC is very low when the HIV-positive partner is on ART. Further follow-up of a larger sample size is required to accurately delineate any residual risk.

1020 Seminal Shedding of CMV and HIV Transmission Among Men Who Have Sex With Men

Sara Gianella Weibel[1]; Konrad Scheffler[1]; Sanjay Mehta[1]; Susan J. Little[1]; Lorri Freitas[2]; Sheldon R. Morris[1]; David M. Smith[1]
[1]University of California San Diego, La Jolla, CA, US; [2]County of San Diego Public Health Services, San Diego, CA, US

Background: Almost all HIV-infected men who have sex with men (MSM) in San Diego are seropositive for cytomegalovirus (CMV) and approximately half shed seminal CMV at any given time. This shedding is associated with detectable HIV in semen, enhanced HIV replication, up-regulation of CCR5, and ultimately with HIV transmission. Here, we estimate the population attributable risk (PAR) of CMV shedding to the number of HIV transmissions among MSM living in San Diego. We compare this estimate to the PAR for other sexually transmitted infections (STIs)- gonorrhea, syphilis, Chlamydia and herpes simplex virus type 2 (HSV-2).

Methods: We estimate relative risks for CMV shedding, bacterial STI and HSV-2 based on the number of transmissions observed in two studies of 47 epidemiologically and phylogenetically linked MSM pairs where the potential source partner was HIV-infected while the potential recipient partner was initially HIV-uninfected. PAR estimates were calculated by combining these estimates with the risk factor prevalences of seminal CMV shedding, bacterial STI, HSV-2 serostatus, and incidence of HIV among MSM in San Diego.

Results: In 2013, 339 HIV diagnoses among MSM were reported in San Diego. Using data collected from MSM in San Diego, we estimate that: 51% shed CMV in their semen at any time, prevalence of bacterial STI is 15% and seropositivity for HSV-2 is 41%. Transmission of HIV from the potential source partner to recipient partner occurred in: (i) 53% versus 25% (source partner shedding CMV versus not shedding CMV), (ii) 100% versus 37% (source partner with bacterial STI versus no STI), (iii) 42% versus 28% (source partner HSV-2 seropositive versus seronegative). None of the potential source partners had detectable HSV-2 in semen. Based on these data, we calculate that over a third of HIV transmissions among MSM in San Diego (37%) could be attributable to CMV shedding (111 transmission events), compared to no more than 21% for bacterial STI (62 events) and 17% for HSV-2 (51 events).

Conclusions: This study supports the hypothesis that CMV shedding among MSM contributes to a large proportion of HIV transmissions in San Diego. Such contribution seems to be larger than that of bacterial STI and HSV-2. Confirming this hypothesis would require a large randomized placebo-controlled clinical trial, which will be difficult with currently approved anti-CMV therapies given their inherent toxicities, but newer anti-CMV therapies and vaccines may hold promise.

1021 Risk Factors for Acute and Early HIV Infection Among MSM in San Diego, 2008–2014

Martin Hoenigl; Christy M. Anderson; Sanjay Mehta; Nella L. Green; Davey M. Smith; Susan Little
University of California San Diego, San Diego, CA, US

Background: Men who have sex with men (MSM) presenting for HIV screening may represent a sub-segment of the MSM population at higher risk for acquisition of HIV infection.

Methods: We analyzed risk behavior reported for the 12 months prior to testing in MSM receiving the "Early Test", a community-based, confidential acute and early HIV infection (AEH) screening program in San Diego, CA, between April 2008 and July 2014. Analyses were performed using Chi-Square and Mann Whitney U test as well as Cox regression. 14 explanatory variables were included in the final multivariable model and selected with a forward stepwise procedure.

Results: A large cohort was analyzed (n=14,612) and 8935 (61%) of those were MSM, and 200 MSM (2.3%; 219 newly diagnosed chronically infected MSM were excluded) were diagnosed with AEH. Individuals with AEH were significantly younger (median 30 [IQR 25-40] vs. 33 [IQR 27-43], p=0.001) and reported significantly more male sex partners (median 10 [IQR 5-20] vs. 5 [IQR 3-10], p<0.001) than those with negative test results. No differences were found with regard to race or ethnicity.

Prevalence rates by risk behavior are depicted in the table. Interestingly, unprotected receptive anal intercourse (URAI) was associated with only a slight elevation of AEH prevalence (3.11% vs. 2.3%), which is similar to only reporting 5 or more male partners (3.06% vs. 2.3%). However, we found a dose response with number of male partners when combining URAI (URAI and 3 male partners was 3.4%, URAI and 5 male partners 3.71% and URAI with 10 partners was 4.29%). Therefore, the combination of URAI and 5 or more (i.e. above the median) male partners was chosen for our model, and UARI with a HIV positive male was the strongest predictor of seroconversion, followed by number of male partners, the combination of URAI and 5 or more male partners, syphilis diagnosis within last 12 months and methamphetamine use.

Risk factor/Risk behavior (within 12 months prior to test)	Prevalence of acute or early HIV infection per risk behavior			Univariate COX regression analysis			Multivariable COX regression analysis		
	Prevalence of acute/early HIV/ individuals that reported the risk	Prevalence (percent)	P value*	HR	95% CI	p value	HR	95% CI	p value
10 or more male partners	110/2909	3.8%	<0.001	2.308	1.747-3.05	<0.001			n.s.
Number of Male partners	-	-	<0.001	1.005	1.003-1.006	<0.001	1.003	1.001-1.005	0.002
URAI and 5 or more male partners	130/3500	3.7%	<0.001	2.62	1.959-3.503	<0.001	1.969	1.459-2.658	<0.001
Intercourse with HIV positive male	99/2457	4%	<0.001	2.65	2.008-3.497	<0.001			n.s.
RAI with HIV positive	74/1072	6.9%	<0.001	4.417	3.312-5.889	<0.001	3.121	2.301-4.234	<0.001
URAI with IDU	14/142	9.9%	<0.001	5.505	3.194-9.487	<0.001			n.s.
URAI with sexworker	7/123	5.7%	0.011	3.741	1.758-7.963	0.001			n.s.
STD Chlamydia infection	14/366	3.8%	0.046	1.741	1.011-2.997	0.064			n.s.
STD Syphilis	15/167	9%	<0.001	4.6	2.717-7.787	<0.001	3.039	1.786-5.169	<0.001
STD Gonococcal infection	23/530	4.3%	0.001	1.97	1.276-3.042	0.002			n.s.
Methamphtamine, not injected	37/601	6.2%	<0.001	3.517	2.46-5.027	<0.001	2.066	1.406-3.037	<0.001
Ecstasy	36/899	4%	<0.001	1.97	1.373-2.827	<0.001			n.s.
GHB	29/449	6.5%	<0.001	3.599	2.427-5.337	<0.001			n.s.
IVDU Shared Needles	13/216	6%	<0.001	2.326	1.325-4.082	0.003			n.s.

Abbreviations: RAI, receiptive anal intercourse; GHB, gamma hydroxy-butyric acid; IVDU, intravenous drug user; STD, sexual transmitted disease; URAI, unprotected receiptive anal intercourse
* Calculated using Chi-square or Mann Whitney U test.

Conclusions: We established a multivariate model for predicting risk of AEH infection in a cohort of mostly high-risk MSM undergoing HIV screening in central San Diego. We found that while URAI alone was associated with slightly increased AEH risk, the combination of URAI and number of male partners may be a more useful predictor of AEH. Such results may help to better focus and prioritize prevention resources in similar US metropolitan populations.

1022 Influence of Voluntary Repeat HIV Testing on Sexual Risk Behavior Among MSM

Martin Hoenigl; Davey M. Smith; Christy M. Anderson; Nella L. Green; Sanjay Mehta; Susan J. Little

University of California San Diego, San Diego, CA, US

Background: Currently, the CDC recommends that high-risk groups, like sexually active men who have sex with men (MSM), receive HIV testing and counseling every 3 to 6 months. We hypothesized that access to free and convenient HIV nucleic acid testing (NAT) may serve as a driver to increase high risk behaviors in HIV uninfected persons over time.

Methods: We evaluated MSM individuals who enrolled in the "Early Test", a community-based, confidential HIV screening program that includes NAT in San Diego, CA, between April 2008 and July 2014. We compared the baseline risk-taking behaviors in the 12 months prior to testing between repeat and once-only testers and then analyzed change in risk behaviors over time (i.e. dose response for testing) in repeat testers using McNemara test.

Results: After exclusion of testers diagnosed with HIV at the first test, 8604 MSM were included in the analysis: 5402 (63%) single-testers and 3202 (37%) repeat-testers. At baseline, repeat-testers reported significantly more male partners and more unprotected receptive anal intercourse (URAI), when compared to single-testers (all p<0.001).

In 2466 repeat-testers (median time between first and last test 723 days, IQR 410-1205; individuals with <183 days between tests were excluded) risk behaviors reported at the first and last test were compared; see table.

Evaluating for a dose-response of risk behaviors by number of tests, MSM with 2-3 tests (n=1387, median time between first/last test 503 days) were compared to those with 4-5 tests (n=571, 844 days) and those with >5 tests (n=508, 1333 days). The reported risk increased proportional with number of tests: a. URAI with a HIV positive man (2-3 tests= +2.75% absolute [+69.1% relative]; 4-5 tests= +3.48% [+57.6%], >5 tests= +9.47% [+423%]), b. URAI and 10 or more male partners (2-3 tests= +2.38% [+9.8%], 4-5 tests +4.82% [+19.6%], >5 tests= +5.08% [+17.6%]), c. non-intravenous drug usage (2-3 tests= +6.7% [+29.1%], 4-5 tests= +5.95% [+25.4%], >5 tests= +13.19% [+69.8%]), and d. shared needles with drug use (2-3 tests= +1.87% [+170%], 4-5 tests= +1.52% [+79.2%], >5 tests= +3.23% [+734%]).

Risk factor/Risk behavior (within 12 months prior to test)	FIRST TEST		LAST TEST		
	Individuals reporting risk	Percentage	Individuals reporting risk	Percentage	P value using McNemara test
10 or more male partners	851/2466	62.53%	1574/2466	63.83%	<0.001
URAI	1629/2439	66.79%	1620/2456	65.96%	n.s.
URAI and 10 or more male partners	621/2453	25.31%	710/2464	28.81%	<0.001
URAI with HIV positive male	93/2256	4.12%	201/2390	8.41%	<0.001
URAI with CSW	11/2403	0.46%	21/2435	0.86%	n.s.
URAI with IDU	10/2404	0.42%	28/2431	1.15%	0.026
Gonorrhoea	138/2466	5.6%	186/2466	7.54%	0.004
Syphilis	50/2466	2.03%	46/2466	1.87%	n.s.
Any STD	313/2466	12.69%	342/2466	13.87%	n.s.
Shared needles	26/2250	1.16%	76/2353	3.23%	<0.001
IVDU	305/2466	12.37%	336/2466	13.63%	ns
Non-intravenous recreational drug use (i.e. Methamphetamine, Cocaine, Poppers, GHB, Ketamine, XTC)	549/2466	22.26%	743/1723	39.13%	<0.001

Abbreviations: CSW, community sex worker; GHB, gamma hydroxy-butyric acid; IVDU, intravenous drug user; n.s., not significant; STD, sexual transmitted disease; URAI, unprotected receiptive anal intercourse; XTC, Ecstasy

Conclusions: San Diego MSM repeatedly screened for HIV with combined serologic and NAT, practice higher sexual risk behavior than once-only testers. These results support the hypothesis that testing may reinforce ongoing high-risk behaviors in the absence of negative feedback (i.e., positive HIV test). Future studies will be needed to assess causality between testing and change in risk behavior.

1023 HIV-Positive MSM With Unsuppressed Viral Load Are More Likely to Engage in Risky Sex: Vancouver, Canada

David Moore[1]; Zishan Cui[1]; Nathan J. Lachowsky[1]; Henry F. Raymond[2]; Eric Roth[3]; Asheligh Rich[1]; Paul Sereda[1]; Julio Montaner[1]; Mark Gilbert[4]; Robert Hogg[1]

[1]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; [2]San Francisco Department of Public Health, San Francisco, CA, US; [3]University of Victoria, Victoria, Canada; [4]BC Centre for Disease Control, Vancouver, Canada

Background: Treatment as Prevention has been actively promoted in British Columbia (BC) as an approach to controlling the local HIV epidemic. We examined the prevalence and characteristics of HIV positive participants with unsuppressed viral load (VL) in a sample of MSM from Vancouver, BC.

Methods: Participants were aged ≥16 years, male-identified, had sex with a man in the past six months and enrolled from February 25, 2012 – February 28, 2014. Individuals were recruited using respondent driven sampling (RDS) through referrals from peers who previously participated with multiple waves of recruitment to reach different social

networks. Seeds were recruited from community agencies and contacts or through advertisements on mobile smartphone applications or websites. Participants completed a self-administered computer-based survey and a nurse-administered point-of-care HIV test. We also conducted VL and CD4 cell counts for HIV positive participants. Risky sex was defined as condomless anal sex with a known HIV negative or unknown serostatus partner in the past 6 months. We performed multivariate logistic regression using RDS weighted variables to examine factors associated with having an unsuppressed VL (≥200 copies/mL).

Results: We recruited 719 participants, of whom 119 (16.6%) were seeds. The median age was 33 years (IQR 26 - 47). With RDS adjustments, 67.9% identified as Caucasian, 10.9% as Aboriginal, 9.7% as Asian, 6.9% as Latin American and 4.6% as other ethnicities. 53.8% of the sample had a self-reported income of <$15,000 per year. The RDS adjusted HIV prevalence was 23.0%. A total of 36(18.6%) of 199 HIV-positive participants had an unsuppressed VL. Of these, 4 participants had previously undiagnosed HIV infection, 16 were not receiving ART and 16 were receiving ART but were not suppressed. Unsuppressed VL was independently associated with income <$15,000 (adjusted odds ratio [AOR] = 4.26; 95% Confidence Interval [CI] 1.44 – 12.6), use of methamphetamine in the past 6 months (AOR = 6.11; 95% CI 2.43-15.3), non-Caucasian ethnicity (AOR=5.21; 95% CI 2.02-13.3) and risky sex (AOR = 2.12; 95% CI 1.14-7.52).

Conclusions: Despite a high prevalence of HIV, few individuals in our sample of MSM had unsuppressed VL. However, participants with unsuppressed VL were also more likely to report risky sex. Our data suggest a current leading edge of HIV transmission among low-income MSM in association with methamphetamine use.

1024 Substance Use, Mental Health, and HIV Risk Behavior Among MSM in Vancouver, Canada

Nathan J. Lachowsky[1]; Zishan Cui[2]; Asheligh Rich[2]; Paul Sereda[2]; Thomas L. Patterson[3]; Trevor Corneil[1]; Mark Gilbert[4]; Eric Roth[5]; Robert Hogg[6]; David Moore[1]

[1]University of British Columbia, Vancouver, Canada; [2]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; [3]University of California San Diego, San Diego, CA, US; [4]Ontario HIV Treatment Network, Toronto, Canada; [5]University of Victoria, Victoria, Canada; [6]Simon Fraser University, Burnaby, Canada

Background: Syndemic factors (e.g., substance use and mental health) are associated with HIV risk among MSM, but evidence examining both is mixed. The objectives of this study were to develop population-weighted estimates of self-reported substance use and doctor-diagnosed mental health conditions among MSM in Vancouver and to determine how these factors were associated with HIV risk.

Methods: Participants were sexually active men aged ≥16 years recruited using Respondent-Driving Sampling (RDS). Participants completed a self-administered computer-based survey, including substance use in the past 6 months; problem drinking was assessed using Alcohol Use Disorders Identification Test (AUDIT) and depression and anxiety using Hospital Anxiety and Depression Scale (HADS). All analyses were weighted given use of RDS. Manual backward-stepwise multivariate logistic regression was used to examine independent associations with risky sex (defined as unprotected anal intercourse with a known serodiscordant or unknown serostatus partner in the past 6 months).

Results: Of 719 participants, 23.0% were HIV-positive, 67.8% were White, and median age was 33 years (IQR 26-47). Over half (52.0%) of MSM reported any lifetime doctor-diagnosed mental health condition (of whom 46.1% were currently receiving treatment): depression 42.2%, anxiety 25.8%, bipolar disorder 5.8%, alcohol dependency 7.0% and other drug dependency 14.7%. Of all MSM, HADS depression scores were borderline for 67.1% and abnormal for 10.3%, HADS anxiety scores were borderline for 37.1% and abnormal for 47.8%, and AUDIT scores indicated harmful use for 5.5% and possible dependence for 7.8%. Substances used include: crystal meth weekly 5.8%, poppers weekly 6.4%, any viagra 16.7%, any LSD 5.5%. One-third of MSM (35.9%) reported risky sex, which was positively associated with greater HADS depression scores (adjusted odds ratio [AOR]= 1.23 [95% confidence interval 1.10-1.38]), weekly crystal meth use (AOR=3.24[1.31-8.05]), weekly poppers use (AOR=3.19[1.53-6.64]), any viagra use (AOR=2.86[1.79-4.58]), Aboriginal (AOR=2.85[1.53-5.31]) or Latin American (AOR=7.94[3.97-15.89]) vs White ethnicity, and annual income >$30,000 (AOR=1.67[1.12-2.52]). Decreased odds of risky sex were associated with any LSD use (AOR=0.23[0.09-0.56]) and always asking partners their HIV status (AOR=0.33[0.20-0.54]).

Conclusions: Mental health conditions were prevalent; depression and substance use were independently associated with risky sex alongside ethnic and income disparities.

1025 Electronic and Online Innovations in Respondent-Driven Sampling Methodology

Nathan J. Lachowsky[1]; Allan Lal[2]; Zishan Cui[2]; Asheligh Rich[2]; Paul Sereda[2]; Henry Fisher Raymond[3]; Jamie I. Forrest[1]; Eric Roth[4]; Robert Hogg[2]; David Moore[1]

[1]University of British Columbia, Vancouver, Canada; [2]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada; [3]University of California San Francisco, San Francisco, CA, US; [4]University of Victoria, Victoria, Canada

Background: HIV research has increasingly employed Respondent-Driven Sampling (RDS) to access and recruit "hidden" populations, such as MSM. Traditional RDS selects "seeds" (initial participants) in-person and provides participants with a limited number of paper coupons for onward recruitment. The objectives of this study were to explore the impact of online and electronic RDS innovations on differences between 1) MSM in recruitment chains of online VS offline seeds and 2) MSM who redeemed electronic VS paper coupons.

Methods: Participants were MSM aged ≥16 years recruited using RDS from Feb 2012 – Feb 2014 to complete a self-administered computer-based survey. Seeds were selected online (e.g., Grindr, social media) or offline (e.g., community agency, social group) and recruitment coupons were electronic or paper. All analyses used RDS weights. Manual backward-stepwise multivariate logistic regression was used to examine factors associated with 1) being in a recruitment chain started from an online seed VS not and 2) redeeming an e-coupon VS paper.

Results: A sample of 719 MSM was recruited from 119 seeds (85 online, 34 offline). Of the 600 non-seeds, 283 MSM (47.2%) were in recruitment chains of online seeds, which had smaller network sizes than offline seeds (OR=0.99, p<0.01). MSM from an online seed's recruitment chain were more likely to be HIV-negative (adjusted odds ratio, AOR=4.18 with [95% Confidence Intervals 2.60-6.71]), be Latin American VS White (AOR=3.69[1.20-11.33]), be an immigrant (refugee or work/student visa) VS born in Canada (AOR=3.88[1.23-12.27]), have been out for 11-21 VS 1-4 years (AOR=2.45[1.37-4.37]), have a regular partner (AOR=1.75[1.11-2.75]), prefer to bottom VS be versatile (AOR=1.87[1.16-2.99]), and report 201-500 Facebook friends VS >500 (AOR=1.82[1.08-3.07]). Of all participants given coupons (n=644), 75.3% chose only paper, 17.8% chose only e-coupons, and 6.9% chose a mix. MSM who redeemed an e-coupon to participate (n=93, 11.9%) were more likely to be employed (AOR=2.66[1.26-5.64]), be homeless (AOR=12.25[2.78-53.96]), be out at work (AOR=4.93[1.94-12.53]), be out for 1-4 VS 11-21 years (AOR=2.84[1.22-6.62]), be in a common law relationship / married (AOR=2.76[1.02-7.46]), have no recent anal sex (AOR=6.07[1.80-20.51]), have recent female sexual partners (AOR= 3.03[1.18-7.78]), and be circumcised (AOR=2.60[1.36-4.98]).

Conclusions: Innovative use of online seed selection and recruitment e-coupons may assist in reaching MSM who are often omitted in such studies.

1026 Incident Symptomatic Gonorrhea Infection Among Men Who Have Sex With Men, Thailand

Marcel E. Curlin[1]; Sarika Pattanasin[1]; Pikunchai Luechai[1]; Anuwat Sriporn[1]; Jaray Tongtoyai[1]; Eileen F. Dunne[1]; Wichuda Sukwicha[1]; Oranuch Kongpechsatit[1]; Pachara Sirivongrangson[2]; Timothy Holtz[1]

[1]US Centers for Disease Control and Prevention (CDC), Apo, US; [2]Thai Ministry of Public Health, Nonthaburi, Thailand

Background: Neisseria gonorrhoeae (NG) infection may increase the risk of HIV acquisition and transmission among men who have sex with men (MSM). We analyzed NG infection at baseline and factors associated with incident symptomatic NG infection among MSM enrolled in the Bangkok MSM Cohort Study (BMCS).

Methods: Sexually-active Thai MSM aged ≥18 years from the Bangkok metropolitan area were enrolled in the BMCS during 2006-2010 and followed every 4 months for 3-5 years. At baseline, participants were screened for rectal and urethral NG and Chlamydia trachomatis (CT) infections using nucleic acid amplification testing (NAAT). At every visit, participants answered questions about sexual behaviors in the past four months using computer-assisted self-interview, underwent physical examination, and had specimens

collected for HIV testing. Symptomatic participants (i.e. men with urethral or anal discharge, dysuria or rectal pain) were tested for NG infection by NAAT and Gram stain from rectal or urethral specimens. Syphilis testing was performed annually. We calculated NG incidence per 100 Person-Years (PY) by survival analysis, and determined factors associated with NG infection using Cox regression.

Results: Among 1,595 participants who had a specimen at enrollment, the prevalence of rectal and urethral NG was 6.1% and 1.8%, respectively. Of the 1,450 participants for whom data were available for at least one follow-up visit, 119 had NG infection, including 97 (81.5%) with urethral infection and 22 (18.5%) with rectal infection. Forty-one (34.4%) participants had repeat infections at either site, with a median time to repeat infection of 294 days (Interquartile range: 175-461 days). The incidence rate of NG infection was 2.0 per 100 PY. Significant factors associated with incident NG infection were completion of 60 months of follow-up (Adjusted Hazard Ratio, AHR, 1.7), being circumcised at baseline (AHR 0.4), report of condomless insertive-only anal intercourse at baseline (AHR 2.5), report of a casual sex encounter at home at baseline (AHR 1.7), prevalent or incident HIV infection (AHR 1.6), prevalent or incident syphilis infection (AHR 1.8), and CT infection at baseline (AHR 1.9).

Conclusions: Incident NG infection among BMCS participants was associated with high risk sexual behaviors, co-infection with HIV or other STIs, and being uncircumcised. Repeat NG infections were common and imply ongoing high risk behavior and STI/HIV transmission risk within this population.

WEDNESDAY, FEBRUARY 25, 2015

Session P-W4 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Transmission Through Needles and Heterosexual Contact

1027 Occupationally Acquired HIV Infection by Healthcare Personnel–United States, 1985-2013

M Patricia Joyce; David Kuhar; John T. Brooks

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: Since 1991, CDC has investigated all cases of HIV infection reported as acquired occupationally by healthcare personnel (HCP). We reviewed CDC data to update the last report on this subject from 2003, noting that since 1987 CDC has recommended use of standard precautions to prevent HIV exposures and since 1990 occupational post-exposure prophylaxis with antiretrovirals to prevent infections.

Methods: Investigations were led by state HIV surveillance staff with CDC assistance. HCP were defined as anyone working in healthcare settings, including but not limited to physicians, nurses, laboratory personnel, students, trainees, and support staff whether paid or not paid. A confirmed case of infection was defined as occupationally acquired if seroconversion in the HCP was temporally related to a specific exposure to a HIV-positive source and no other temporally related HIV exposures had occurred. A possible case was defined as an infection in a HCP found to be HIV seropositive and whose job duties may have exposed them to HIV but who lacked both a known and documented workplace exposure and any nonoccupational risk.

Results: During 1985-2013, 58 confirmed (figure) and 150 possible cases of occupationally acquired HIV by HCP were reported to the CDC. Among the 58 confirmed cases, the routes of exposure were percutaneous puncture or cut (n=49), mucocutaneous exposure (n=5), both percutaneous and mucocutaneous exposure (n=2), and unknown (n=2). The exposures were to HIV-infected blood (n=49), concentrated virus in laboratories (n=4), visibly bloody body fluid (n=1), and unspecified body fluids (n=4). Since 1999, only one confirmed case has been reported.

Conclusions: Confirmed cases of occupationally acquired HIV require documented seroconversion temporally related to a specific exposure. Occupational acquisition of HIV infection by HCP is now exceedingly rare**.**

1028 Analyzing Trends in HIV Risks for Injection Drug Users by Respondent-Driven Sampling

Kathleen A. Brady; Tanner B. Nassau; Jennifer Shinefeld; Catherine Mezzacappa

Philadelphia Department of Public Health, Philadelphia, PA, US

Background: Philadelphia new HIV cases among IDU declined 80% from 2006-2013 with only 5% of new HIV cases in 2013 classified as IDU. We analyzed National HIV Behavioral Surveillance (NHBS) data among IDU to determine predictors of sharing injection equipment among IDUs and to evaluate trends to illuminate both past successes and future potential means to reduce HIV incidence among IDUs.

Methods: NHBS is a structured interview project conducted in high-risk populations utilizing respondent-driven sampling. Sharing any injection equipment in the past 12 months was the primary outcome. Predictor variables included race/ethnicity, age, education (< or ≥ high school), primary drug (heroin, cocaine or both) and needle source (needle exchange program (NEP), dealer, multiple or other) were compared in the 2005, 2009, and 2012 NHBS in Philadelphia. Data were weighted based on respondent's injection network size. A multivariate logistic regression model was constructed using predictors which were found to be significant in cycle specific models plus a variable for time. Additionally, a Cochran-Armitage test for trend was performed to determine significant changes in sharing behaviors over time.

Results: 483, 525 and 554 participants were interviewed in cycles 1-3. There was no statistically significant trend over time with 47.6%, 64.4% and 54.4% of participants reporting any sharing in the last 12 months. Tests for trends showed that sharing increased significantly in IDUs age 18-34 years (p=0.018), females (p=0.004) and those who obtained their needles from a dealer only (p<0.001). In the final multivariate logistic regression, blacks (OR 0.39, 95%CI: 0.30-0.51) and Latinos (OR 0.64, 95%CI: 0.44-0.92) were significantly less likely to share compared to whites. IDU that used a NEP (<.0001) were less likely to share than IDU whose source of needles were a dealer or multiple sources. Year, education and primary injection drug were also found to be significant predictors of sharing (Figure).

N=1562	Weighted Percent Total(%)	OR(95%CI)	p
Year			
2005	30.9	1.0	
2009	33.6	1.32(0.99-1.76)	0.0595
2012	35.5	0.90(0.68-1.19)	0.4574
Age			
≥45	24.4	1.0	
18-34	30.5	0.99(0.73-1.35)	0.9659
35-44	45.1	0.85(0.66-1.10)	0.2108
Gender			
Male	68.5	1.0	
Female	31.5	1.08(0.85-1.37)	0.5195
Ethnicity			
White	39.1	1.0	
Black	49.2	0.39(0.30-0.51)	<.0001
Latino	11.7	0.64(0.44-0.92)	0.0164
Education			
<HS	36	1.0	
>=HS	64	0.64(0.51-0.81)	0.0001
1°Drug			
Heroin	73.3	1.0	
Cocaine	7.5	0.93(0.61-1.42)	0.7501
Speedball	19.2	1.43(1.07-1.90)	0.0151
Source			
NEP	18.3	1.0	
Dealer	9.3	1.64(1.07-2.51)	0.0235
Other	10.7	0.87(0.58-1.31)	0.5117
Multiple	61.7	1.98(1.48-2.65)	<.0001
Non-Inject –12 mon.	67.7	1.16(0.94-1.50)	0.1553
Drug Treat—12 mon.	36	1.12(0.89-1.41)	0.3425

Conclusions: Further increasing the utilization of NEPs in persons of all races, females and IDU age 18-34 may reduce the likelihood of sharing any injection equipment and may help to further decrease HIV transmission. Surprisingly, we did not observe a declining trend in the sharing of injection equipment in IDU despite a decline in HIV incidence over the course of the NHBS cycles. Further analysis should focus on barriers to the use of NEPs and other risk behaviors that may influence HIV transmission among IDU.

1029 Sexual Transmission of HIV and Possible Underreporting of Drug Use in Kazakhstan

Anna Deryabina; Padmaja Patnaik; Charon Gwynn; Wafaa M. El-Sadr
ICAP at Columbia University, Almaty, Kazakhstan

Background: National data in Kazakhstan suggest that ≥50% of new HIV infections occur in people who inject drugs (PWID) through contaminated needles. However, recent trends suggest an increasing role of heterosexual transmission of HIV, possibly among sex partners of PWID. To better understand these trends, we conducted a survey among sex partners of PWID in Kazakhstan.

Methods: A cross-sectional survey was conducted in a convenience sample of sex partners of PWID to determine HIV and HCV seroprevalence and to identify factors associated with HIV. Sex partners were referred by PWID that were recruited through a nationally conducted integrated bio-behavioral survey or from NGOs in Karaganda, Temirtau, Ust-Kamenogorsk and Kostanai - cities with highest rates of sexually transmitted HIV. Recruitment was limited to sexual partners who did not report *current* injection drug use (IDU). Behavioral data were collected through semi-structured interviews. Dried-blood spots were tested for HIV and HCV using ELISA. Multivariate analyses were conducted using logistic regression modeling to identify factors independently associated with HIV.

Results: Of 1,125 sex partners of PWID, 19% were men and 81% women, mean age 32. HIV prevalence in participants was 9.3% in men and 7.0% in women (p>0.05). Those having a PWID partner with known HIV-infection (OR=5.1, 95%CI=2.5-10.7) and those reporting past history of IDU (OR=4.8, 95%CI=2.4-9.6) had a higher likelihood of HIV infection. HIV prevalence was lower among those who reported no past history of IDU (5.2%; p<0.001). HCV prevalence (a possible surrogate for IDU) was high: 51.4% in men and 19.8% in women (p<0.001). Yet only 58.2% of HCV-positive men and 41.1% of HCV-positive women (p<0.001) reported prior history of IDU, suggesting under-reporting of injecting behavior. HIV prevalence was significantly lower (4.0%; p<0.05) in partners of PWID who reported no prior history of IDU and were HCV-negative.

Conclusions: HIV prevalence was high in sexual partners of PWID in Kazakhstan. Sex with HIV-positive PWID was significantly associated with HIV infection. However, high HCV prevalence is those reporting solely current sexual contact with PWID suggests possible underreporting of previous or current IDU likely due to stigma, especially for women. Thus, increase in reported sexually-acquired HIV in the country may represent underreported IDU. Programs for prevention of sexual transmission of HIV should target PWID and their sex partners and address IDU in both groups.

1030 Can We Trust Self-Reported Condom Use? Association Between Reporting Bias and STIs

Hongjie Liu

University of Maryland, College Park, College Park, MD, US

Background: Self-reported condom use has been used for three decades in behavioral research. However, reporting bias and its association with sexually transmitted infections (STIs) including HIV have seldom assessed in large-scale studies. The objectives of this study were to use a biologic measure to validate self-reported condom use and to investigate if reporting bias was associated with syphilis among older female sex workers (FSWs) in China.

Methods: The study was conducted among 1,245 older FSWs who were 35 years old and older in three cities (about 400 per each). Respondent-driving sampling was used to recruited study subjects. Prevalent and active syphilis was tested in blood samples. Prostate-specific antigen (PSA) was tested in vaginal secretion samples. The presence of PSA indicates unprotected sex. If an older FSW reported having had no sex in the past 24 hours and PSA was present, she was classified as having a discordant report on no sex. Similarly, if an older FSW reported having had only protected sex in the past 24 hours, but PSA was present, she was classified as having a discordant report on protected sex.

Results: The prevalence of syphilis was 23% (95%CI: 21-26%) and the rate of active syphilis was 10% (95%CI: 9-12%) among older FSWs. Among 493 older FSWs who reported having had no sex in the past 24 hours, 135 were tested positive for PSA, resulting the proportion of discordant report in no sex was 27%. Among 445 older FSWs who reported having used condoms for every sexual intercourse, 166 were tested positive for PSA, i.e., the proportion of discordant report in protected sex was 37%. After controlling for confounding variables, older FSWs who had prevalent syphilis were more likely to have discordant report in no sex [prevalence ratio (PR) = 1.77; 95%CI, 1.29-2.42)] and in protected sex (PR =1.56; 95%CI, 1.14-2.14) than those who did not have prevalent syphilis. Similarly, older FSWs who had active syphilis were more likely to have discordant report in no sex (PR =1.94; 95%CI, 1.37-2.74) and in protected sex (PR =1.65; 95%CI, 1.12-2.43) than those who did not have active syphilis. Similar results were presented in separated analyses across the three study sites.

Unadjusted and adjusted associations between discordant reports in sex practices HIV knowledge, and attitudes toward condom use

	Discordant report in no sex		Discordant report in protected sex	
	PR***	95% CI	PR	95% CI
Unadjusted				
Prevalent syphilis (yes vs. no)	1.81	1.36-2.42	1.35	1.02-1.80
Active syphilis (yes vs. no)	2.04	1.47-2.84	1.36	0.94-1.96
HIV knowledge	0.92	0.88-0.96	1.04	0.98-1.11
Attitude to condom use	0.97	0.93-1.01	1.06	1.02-1.11
Adjusted in model 1*				
Prevalent syphilis (yes vs. no)	1.65	1.21-2.26	1.44	1.06-1.95
Active syphilis (yes vs. no)	1.84	1.33-2.54	1.50	1.02-2.20
Adjusted in model 2**				
Prevalent syphilis (yes vs. no)	1.77	1.29-2.42	1.56	1.14-2.14
Active syphilis (yes vs. no)	1.94	1.37-2.74	1.65	1.12-2.43
HIV knowledge	0.93	0.88-0.98	1.04	0.97-1.11
Attitude to condom use	0.99	0.95-1.04	1.07	1.02-1.12

*adjusted for socio-demographics (age, education level, marital status, migration status, and interview sites)
**adjusted for socio-demographics, duration of sex work, history of STDs, and self-perceived risk for STIs
***prevalence ratio and 95% confidence interval

Conclusions: Self-reported condom use has strong reporting bias and may not be used as an outcome to measure effectiveness of STI interventions as the bias is also associated with occurrence of STIs. PSA test provides a valid bio-approach for assessing actual condom use and can be used in large scale studies.

1031 Prevalence and Correlates of Exchange Sex Among Low-Income Heterosexual Women in 21 US Cities

Catlainn Sionean; Rashunda Lewis; Lina M. Nerlander; Gabriela Paz-Bailey
On behalf of the NHBS Study Group

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: Female sex workers and other women who exchange sex for money or drugs are at increased risk for HIV infection in many countries; however, little is known about exchange sex among women in the United States. We used data from the 2010 heterosexual cycle of the National HIV Behavioral Surveillance System (NHBS), a cross-sectional survey conducted in 21 US cities with high AIDS prevalence, to estimate the percentage of female participants who received money or drugs from a man in exchange for sex and compare their HIV-related behaviors with those among women who had not exchanged sex.

Methods: Heterosexuals of low socioeconomic status were recruited via respondent-driven sampling, interviewed, and tested for HIV infection. Analyses were limited to female participants with valid interview and HIV test results. We used generalized estimating equations (GEE) to test for associations between exchange sex as the outcome and HIV-related behaviors adjusted for recruitment chain, demographics and network size. We present adjusted prevalence ratios (aPR) and 95% confidence intervals (CI).

Results: Among 5507 female participants, 19% had exchanged sex during the past 12 months, among whom the median number of male sex partners during the past 12 months was 6. In multivariable analyses, exchange sex was more common among women who, during the past 12 months: had been homeless (aPR=1.38, 95% CI: 1.24-1.53) vs. not; had been arrested (aPR=1.17, 95% CI: 1.03-1.33) vs. not; used crack cocaine (aPR=1.45, 95% CI: 1.28-1.63) vs not; had been diagnosed with an STD (aPR=1.36, 95% CI: 1.22-1.51) vs. not; had vaginal sex without a condom with 6 or more partners (aPR=2.07, 95% CI: 1.62-2.65) vs. none; had 2 or more new partners (aPR=2.35 95% CI: 1.98-2.79) vs. none; and women whose last sex partner was at least 10 years older (aPR=1.58, 95% CI: 1.40-1.77) vs. not, was HIV+ or of unknown status (aPR=1.20, 95% CI: 1.07-1.35) vs. negative, had ever been incarcerated (aPR=1.25, 95% CI: 1.11-1.40), or ever had sex with another man (aPR=1.16, 95% CI: 1.04-1.30). Exchange sex was not independently associated with HIV testing, HIV infection, or injection drug use.

Conclusions: Among low-income women sampled from select US cities with high rates of poverty and HIV, exchange sex was common overall and particularly among those whose economic circumstances, behaviors, and sex partners indicate increased risk for HIV infection. HIV prevention efforts may be enhanced by outreach to heterosexual women who exchange sex.

1032 HIV and STIs Among Transgendered Populations: Four Country Survey From Central America

David Ham[1]; Sanny Y. Northbrook[2]; Sonia Morales-Miranda[3]; Maria Elena Guardado[4]; Mary Kamb[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]CDC Central America Region, Guatemala City, Guatemala; [3]HIV Unit of Center for Health Studies, Del Valle University of Guatemala, Guatemala City, Guatemala; [4]TEPHINET/ The Taskforce for Global Health Inc., Guatemala City, Guatemala

Background: In Central America, men who have sex with men (MSM) are estimated to have the highest HIV prevalence of any group; however little is known about HIV and STIs among male-to-female transgendered (MTFTG) individuals. We sought to characterize HIV and STI prevalence among MTFTG in 4 Central American countries participating in special surveillance studies.

Methods: We used data from a standardized behavioral and biological surveillance survey administered in 4 countries: El Salvador (2007-2008), Guatemala (2012), Honduras (2012), and Nicaragua (2009-2010). Investigators used respondent-driven sampling (RDS) to recruit MSM, defined as a man reporting anal or oral sex with a man in the previous 12 months; a separate question asked about MTFTG identification. Audio computer-assisted self-interviews were used to measure behavioral risks, and biologic specimens were used to measure HIV (EIA and confirmatory testing), syphilis (RPR/TPPA), HSV-2 (EIA), gonorrhea, chlamydia, *Mycoplasma genitalium* and trichomonas (nucleic acid amplification tests based on urine and/or anal and pharyngeal swabs). We used raw unadjusted RDS data on STIs (3 countries, excluding Guatemala) and HIV (all 4 countries).

Results: Of 2,746 MSM surveyed in the 4 countries, 405 (15%) self-identified as MTFTG. Median age was 24 years for MTFTG and 23 years for non-transgendered MSM. Prevalence of specific STIs among MTFTG ranged from 14–23% for TPPA confirmed syphilis, 54–81% for HSV-2, 4–7% for gonorrhea (GC), 5–19% for chlamydia (CT), 2–3% for mycoplasma (M Gen), and 0–1% for trichomonas (Trich) (Table 1). Prevalence of at least one "curable STI" (syphilis, gonorrhea, chlamydia, mycoplasma, or trichomonas) ranged from 22–36% among MTFTG compared to 15–25% among MSM. HIV prevalence among MTFTG ranged from 10% (6/62 tested in Nicaragua) to 28% (23/83 tested in El Salvador). Overall HIV prevalence in MTFTG (4 countries) was 22% (86/391) compared to 11% (232/2199) among MSM survey participants. After adjusting for age and country of origin, MTFTG were almost twice as likely to have HIV as MSM (Adjusted Prevalence Ratio = 1.9; 95% Confidence Interval =1.5, 2.4]).

Table 1. Central American HIV and STI prevalence by high risk group

		Syphilis (RPR +)			RPR confirmed probable Active Syphilis (RPR+/TPPA +)			M Gen (urine)	Trich (urine)	HSV-2 (serology)	HIV	Any curable STI
		Total	<8 titer	>=8 titer	Total	<8 titer	>=8 titer					
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
El Salvador												
(2007-2008)	MTFTG	14/84 (16.7)	6/ 84 (7.1)	7/84 (8.3)	12/84 (14.3)	4/84 (4.8)	7/84 (8.3)	2/79 (2.5)	1/79 (1.3)	62/84 (73.8)*	23/83 (27.7)*	19/88 (21.6)
	MSM	68/620 (11.0)	32/620 (5.1)	32/620 (5.1)	58/620 (9.4)	26/620 (4.2)	29/620 (4.7)	14/583 (2.4)	6/584 (1.0)	276/620 (44.5)	73/627 (11.6)	112/725 (15.5)
Nicaragua												
(2009-2010)	MTFTG	16/62 (25.8)*	9/62 (14.5)	7/62 (11.3)	14/62 (22.6)*	7/62 (11.3)	7/62 (11.3)	1/62 (1.6)	0/62 (0)	50/62 (80.6)*	6/62 (9.7)	21/62 (33.9)*
	MSM	40/590 (6.8)	21/590 (3.5)	19/590 (3.2)	40/590 (6.8)	21/590 (3.5)	19/590 (3.2)	15/590 (2.5)	4/590 (0.7)	249/590 (42.2)	45/590 (7.6)	91/591 (15.4)
Guatemala												
(2012)	MTFTG										29/125 (23.2)*	
	MSM										46/438 (10.5)	
Honduras												
(2012)	MTFTG	20/124 (16.1*)	11/124 (8.9)	9/124 (7.3)	19/124 (15.3)*	10/124 (8.1)	9/124 (7.3)	3/126 (2.4)	0/126	67/124 (54.0)*	28/121 (23.1)*	46/127 (36.2)*
	MSM	36/553 (6.5)	14/553 (2.5)	22/553 (4.0)	35/553 (6.3)	13/553 (2.4)	22/553 (4.0)	31/562 (5.5)	5/562 (0.9)	195/553 (35.3)	68/544 (12.5)	145/579 (25.0)
Combined HIV prevalence												
	MTFTG										86/391 (22.0)*	
	MSM										232/2199(10.6)	

		GC urine	CT urine	GC rectal	CT rectal	GC Pharyngeal	CT Pharyngeal	GC any site	CT any site			
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)			
El Salvador												
(2007-2008)	MTFTG	1/79 (1.3)	1/79 (1.3)	2/65 (3.1)	3/64 (4.7)			3/80 (3.8)	4/80 (5.0)			
	MSM	7/584 (1.2)	16/584 (2.7)	16/454 (3.5)	13/448 (2.9)			22/590 (3.7)	28/590 (4.7)			
Nicaragua												
(2009-2010)	MTFTG	0/62 (0)	0/62 (0)	4/54 (7.4)*	4/54 (7.4)			4/62 (6.5)*	4/62 (6.5)			
	MSM	3/590 (0.5)	11/590 (1.9)	8/466 (1.7)	14/466 (3.0)			11/590 (1.9)	25/590 (4.2)			
Honduras												
(2012)	MTFTG	0/126 (0)	2/126 (1.6)	8/113 (7.1)	17/113 (15.0)	2/112 (1.8)	6/112 (5.4)	9/127 (7.1)	24/127 (18.9)			
	MSM	4/562 (0.7)	26/562 (4.6)	18/411 (4.4)	44/411 (10.7)	10/501 (2.0)	13/501 (2.6)	26/566 (4.6)	74/566 (13.1)			

*p<0.05

Conclusions: HIV and other STIs were common among MTFTG participating in the Central American surveys, and HIV prevalence was almost twice that of MSM. Targeted HIV/STI efforts among MTFTG are important to prevent HIV acquisition and transmission in this high risk, highly vulnerable subgroup.

1033 Incidence of Curable Sexually Transmitted Infections Among South African Women Recently Infected With HIV

Jennifer E. Balkus[1]; Marla E. Husnik[1]; Thesla Palanee-Phillips[2]; Ravindre Panchia[3]; Ishana Harkoo[4]; Arendevi Pather[5]; Vaneshree Govender[5]; Marthinette Taljaard[6]; Pamina Gorbach[7]; Sharon Riddler[8]

[1]Fred Hutchinson Cancer Research Center, Seattle, WA, US; [2]University of the Witwatersrand, Johannesburg, South Africa; [3]Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa; [4]CAPRISA/ University of KwaZulu-Natal, Durban, South Africa; [5]Medical Research Council, Durban, South Africa; [6]The Aurum Institute, Klerksdorp, South Africa; [7]University of California Los Angeles, Los Angeles, CA, US; [8]University of Pittsburgh, Pittsburgh, PA, US

Background: Curable sexually transmitted infections (STIs), including chlamydia (CT), gonorrhea (GC), and trichomoniasis (TV) are common among HIV-infected women; however, data are limited for women recently infected with HIV. We assessed the incidence of and risk factors for CT, GC and TV among South African women who acquired HIV while participating in VOICE, a phase IIB randomized trial of daily oral and vaginal chemoprophylaxis for HIV prevention in Ugandan, South African, and Zimbabwean women.

Methods: Women who acquired HIV during VOICE were invited to enroll in MTN-015, a multi-site, prospective cohort study of women who became HIV-infected in Microbicide Trials Network studies. Demographic and sexual behavior data were collected via face-to-face interviews. Participants were tested for STIs (CT/GC using nucleic acid amplification tests and TV using rapid tests) at enrollment, annual visits and when clinically indicated. Treatment was provided according to WHO guidelines. Cox proportional hazards models stratified by site were used to assess baseline correlates of CT, GC or TV infection during follow-up, each as separate outcomes. Multivariable models were adjusted for age and other factors that were associated with STI acquisition in univariate models ($p \leq 0.1$).

Results: Of 339 eligible South African women from VOICE, 237 enrolled in MTN-015 and 207 had CT, GC, or TV results at enrollment and during follow-up. Median time from testing HIV+ in VOICE to MTN-015 enrollment was 2.3 months (interquartile range 1.3–3.8). Detection of CT while participating in VOICE was associated with incident CT in MTN-015

(yes=27.1/100 person-years [p-yrs] vs no=6.9/100 p-yrs; adjusted hazard ratio [aHR] 3.7, 95% CI 1.5, 9.3) and younger age trended toward an association (age <25 years=14.6/100 p-yrs vs. ≥25 years=7.6/100 p-yrs; aHR 2.0, 95% CI 0.8, 4.9). Having any curable STI in VOICE (CT, GC, or TV) was associated with incident TV (yes=16.5/100 p-yrs vs. no=4.2/100 p-yrs; aHR 5.6 95% CI 1.7, 18.4). No factors were associated with GC during follow-up. Results were similar in sensitivity analyses that excluded participants with the STI of interest at enrollment from each analysis.

STI	# of infections at MTN-015 enrollment/ # of women in analysis	Prevalence	# of infections in follow-up/p-yrs	Incidence per 100 p-yrs (95% CI)	
CT	31/194	16.0%	32/269	11.9	(8.1, 16.8)
GC	20/195	10.3%	26/272	9.6	(6.3, 14.0)
TV	17/177	9.6%	22/239	9.2	(5.8, 13.9)

Prevalence and incidence of curable STIs among HIV-infected South African women

Conclusions: Curable STI incidence was high among South African women recently infected with HIV, especially among women who had a recent STI. New strategies for STI prevention counseling, screening, and treatment of women and their partners are needed to reduce the burden of curable STIs among recently HIV-infected women in this region.

1034 Population Mobility, Sexual Behavior and Risk of HIV Infection in Sub-Saharan Africa

Laurence Palk; Sally Blower
On behalf of the Center for Biomedical Modeling
David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US

Background: Studies in Sub-Saharan Africa have shown an association between increased mobility and increased levels of sexual behavior, and/or risk of HIV infection. However, these studies have been conducted in countries with low/moderate HIV epidemics. Here we assess the potential impact of mobility on the high-prevalence epidemic in Lesotho, where 27% of women and 18% of men are infected with HIV.

Methods: We analyzed linked demographic, behavioral and HIV infection data from the 2009 Demographic and Health Survey of Lesotho. The response rate was 98% for women, 95% for men. Further, 94% of eligible women and 88% of eligible men were tested for HIV. We quantitatively assessed the mobility of the population. We used a multivariate analysis to determine whether there is an association between mobility and increased levels of sexual behavior and/or risk of HIV infection.

Results: We found that the population of Lesotho is highly mobile: 30% of women and 32% of men made one to four trips in the last year, 18% of women and 21% of men made five or more. Among those who travelled 37% of women and 39% of men were away for at least a month. Individuals who travelled were older than those who did not travel. They were also more likely to be married, employed, live in urban areas and have a higher level of education. In addition they were more likely to have had multiple partners in the last year; odds increased with frequency of travel, see table. Those who made five or more trips were almost twice as likely to have had two or more partners than those who did not travel. Individuals who travelled were also more likely to have concurrent partners than those who did not; odds increased with frequency of travel, see table. However, men who travelled were not more likely to have paid for sex than men who did not travel. Notably, only men who made five or more trips had an increased risk of HIV infection, see table. However, men who traveled infrequently (made one to four trips in the last year), and women who traveled (regardless of the number of trips) did not have an increased risk in comparison with individuals who did not travel.

Odds ratios of HIV infection and sexual risk behavior		Women: Trips away in the last year 0	Women: 1 to 4	Women: 5+	Men: Trips away in the last year 0	Men: 1 to 4	Men: 5+
HIV infected	aOR (95% CI)	1 (REF)	0.91 (0.76-1.09)	1.13 (0.92-1.39)	1 (REF)	1.17 (0.93-1.48)	1.31 (1.01-1.68) *
2 or more sex partners in last year	aOR (95% CI)	1 (REF)	1.64 (1.22-2.21) **	1.97 (1.41-2.73) ***	1 (REF)	1.58 (1.29-1.94) ***	2.00 (1.60-2.50) ***
Concurrent partnership in last year	aOR (95% CI)	1 (REF)	1.79 (1.29-2.49) ***	1.92 (1.33-2.77) ***	1 (REF)	1.33 (1.05-1.68) *	1.76 (1.38-2.25) ***

Table: Adjusted odds ratios (aOR) and confidence intervals (CI) of HIV infection and sexual risk behavior. Odds ratios are calculated adjusting for age, employment status, marital status and education. Stars denote the significance according to the following P-values: *** P <0.001, ** 0.001≤P<0.01, * 0.01≤P<0.05. Concurrent partnerships are calculated amongst those who had sex in the last 12 months.

Conclusions: Population mobility needs to be considered when developing HIV prevention programs. Further, it is essential to target highly mobile men because they may disproportionally contribute to transmission. In Lesotho, and other countries with high levels of mobility (e.g., Zimbabwe, Cameroon and Kenya), it may be more difficult to control HIV epidemics than currently appears.

1035 HIV Transmission Linkage Among Seroconverting Partners in HIV-Discordant Relationships in Kenya

Bhavna H. Chohan[1]; Brandon L. Guthrie[2]; Brian Khasimwa[4]; Stephanie Rainwater[3]; Barbara Lohman-Payne[2]; Rose Bosire[2]; Romel D. Mackelprang[2]; Julie M. Overbaugh[3]; Carey Farquhar[2]
[1]*Kenya Medical Research Institute, Nairobi, Kenya;* [2]*University of Washington, Seattle, WA, US;* [3]*Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US;* [4]*University of Nairobi, Nairobi, Kenya*

Background: A large proportion of HIV-1 transmissions occur in the context of stable, HIV-discordant relationships. Understanding the distribution of infections that originate from within the current partnership (linked) versus from an outside sexual relation (unlinked) is relevant to prevention interventions. We obtained viral sequences from newly HIV-1 infected individuals and their HIV-infected partners at seroconversion to determine the linkage of viral transmissions.

Methods: A cohort of heterosexual HIV-serodiscordant couples in Nairobi, Kenya were followed to identify HIV-1 transmission events. HIV-1 envelope sequences were amplified and sequenced from peripheral blood mononuclear cells obtained from both partners at HIV sereconversion. Phylogenetic trees of viral sequences were constructed using the GTR Substitution Model in BEAST and pairwise genetic distances in PAUP* to assess genetic relationships and determine whether the new infection was linked to the study partner. Seroconversion risk was assessed by Cox proportional hazards regression. Demographic and behavioral factors were compared between the unlinked versus linked transmissions using Chi-square tests student's t-tests.

Results: A total of 12 incident HIV-1 infections occurred in a cohort of 458 HIV-1 serodiscordant couples (1.5/100 person-years). Phylogenetic analysis identified 8 (67%) incident infections as linked transmissions and 4 (33%) as unlinked. Viruses from the linked transmission pairs were closely related and formed monophyletic clusters on a single node in the phylogenetic trees (mean genetic pairwise distance 3.4%; range 0.12-6.23%). The HIV-1 *env* sequences from the unlinked transmission were distantly related and formed polyphyletic clusters (mean genetic distance 13.7%; range 9.22-17.51%). All 4 unlinked HIV transmissions were in males, compared to only 2 (25%) of 8 linked transmissions

(p=0.061). Those with an unlinked transmission reported more lifetime sexual partners (p=0.008) and had partners with a higher CD4 count (p=0.027) than those with a linked transmission.

Conclusions: Nearly a third of the HIV-1 incident infections in this treatment-naïve serodiscordant couple cohort were unlinked transmissions with a high frequency occurring in males consistent with other studies in sub-Saharan Africa. Interventions to prevent HIV transmission in discordant couples should address the risk of infection from an outside sexual partner. This may be particularly important when the uninfected partner is male.

1036 Rising School Enrollment & Declining HIV Risk, 15-19y, Rakai, Uganda, 1994-2013

John Santelli[1]; Sanyukta Mathur[1]; Xiao Yu Song[2]; Tzu-Jung Huang[2]; Ying Wei[2]; Tom Lutalo[3]; Fred Nalugoda[3]; Ronald H. Gray[4]; David Serwadda[3]

[1]New York–Presbyterian University Hospital of Columbia and Cornell, New York City, NY, US; [2]Columbia University–Mailman School of Public Health, New York, NY, US; [3]Rakai Health Sciences Program, Entebbe, Uganda; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

Background: Economic development, family stability, and social policies influence the ability of adolescents to attend school. Likewise, rising school enrollment may shape social developmental transitions and risk for HIV among youth.

Methods: We examined longitudinal quantitative data from the Rakai Community Cohort Study (RCCS) for adolescents (n=11,829 person-rounds for women and 9906 person-rounds for men) from 1994 to 2013 in Rakai, Uganda, and ethnographic data from youth (15-24 years) collected in 2010-11. Longitudinal data were analyzed using *logistic and linear regression with robust estimation* to identify antecedents and consequences of school attendance. Ethnographic data explored social developmental transitions among HIV-infected and HIV-uninfected youth.

Results: School enrollment and household socioeconomic status (SES) rose steadily from 1994 to 2013; orphanhood declined among adolescents after 2004 when ART became available. For young women, school enrollment rose from 25% to 57% and for young men from 34% to 67%. Significant antecedents of school enrollment for adolescent women and men included younger age and (after adjusting for age) higher SES, not being an orphan, being unmarried, and living in a family with fewer children. In qualitative interviews, youth reported lack of money, death of parents, and pregnancy as primary reasons for school drop out. Compared to adolescent women who were not enrolled, school enrollment (adjusting for age) was associated with lower HIV prevalence (6.5% vs. 1.8%) and lower rates of certain HIV risk behaviors including not initiating sexual intercourse (37% vs. 88%), alcohol use in the past 30 days (14% vs. 25%), and consistent condom use with all partners (70% vs. 17%) but not 2+ sexual partners or sexual concurrency. School enrollment has a similar protective association for men, but in addition, young men enrolled is school were less likely to have 2+ sexual partners in the past year (28% vs. 42%) and less likely to be involved currently in sexual concurrency (6% vs. 11%).

Conclusions: Social trends such as rising SES and declining orphanhood contributed to rising school enrollment in Rakai. Rising school enrollment was associated with declines in certain HIV behaviors, although these varied by gender.

1037 Alcohol Use and HIV Risk Factors: Results From the 2011 Uganda AIDS Indicator Survey

George Aluzimbi

CDC Center for Global Health, Division of Global AIDS/HIV, Kampala, Uganda

Background: Uganda has one of the highest per capita alcohol consumption worldwide. Alcohol use has been shown to increase the likelihood of high risk sexual behavior and is associated with HIV infection. We evaluated the association between alcohol use during sex and HIV prevalence in a nationally representative household survey in Uganda.

Methods: The Uganda AIDS Indicator Survey was a population-based household survey designed to produce national and regional estimates of HIV prevalence and risk behavior, conducted February to September 2011. HIV and syphilis serological tests were conducted on all consenting participants. Respondents who were sexually active in the past 12 months were asked if alcohol was consumed by both, either or none of them during sex with most recent sexual partner. We analyzed data from respondents aged 15-59 who had had sex in the past 12 months and had reported consumption of alcohol during sexual intercourse.

Results: A total of 21741 persons were enrolled in the Uganda AIS; 15917 (85.1%) reported being sexually active in the 12 months prior to the survey; and alcohol consumption during most recent sexual activity was reported by 24.0% of men (1719/7133) and 24.1% of women (2123/8775). Condom use at last sexual intercourse was higher among non-drinkers compared to alcohol drinkers (men: 2.6% vs. women: 5.8%). Overall, HIV prevalence was higher in those who consumed alcohol during sex compared to those who did not (men: 10.4% vs. 5.9%; women: 9.5% vs. 7.7%). In adjusted analysis, alcohol use during sex was associated with HIV infection (men: OR= 1.7 [95% CI 1.29-2.15], women: OR=1.3 [CI 1.03-1.59]), syphilis infection (men: OR= 1.7 [95% CI 1.14-2.62], women: OR=1.8 [CI 1.24-2.53]), unprotected sex (men OR=1.7 [CI 1.49-1.98], women OR=1.9 [CI 95% 1.54-2.48]), and paying for sex among men (OR=1.8 [CI 1.42-2.18]). Men who were circumcised (OR=0.5 [CI 0.32-0.78]) were less likely to drink alcohol prior to sexual intercourse.

Conclusions: About 25% of Ugandans consumed alcohol during sex. Alcohol consumption was associated with lower condom use, and higher HIV and syphilis infection. Alcohol interventions should be closely integrated into HIV prevention policy and programming.

1038 Population Attributable Fraction of HIV Due to Alcohol in Fishing Communities, Uganda

Noah Kiwanuka[5]; Ismail Ssekandi[2]; Ali Ssetaala[2]; Annet Nalutaaya[2]; Juliet Mpendo[2]; Paul K. Kitandwe[2]; Jan D. Bont[3]; Pontiano Kaleebu[4]; Nelson K. Sewankambo[5]

[1]Makerere University College of Health Sciences, Kampala, Uganda; [2]UVRI-IAVI HIV Vaccine Program, Entebbe, Uganda; [3]International AIDS Vaccine Initiative, New York, NY, US; [4]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda; [5]Makerere University College of Health Sciences, Kampala, Uganda

Background: Studies have shown that alcohol drinking is associated with HIV risk behaviours, and HIV prevalent and incident infections. We assessed the population attributable fraction (PAF) of incident HIV infections due to alcohol consumption in fishing communities (FC), along Lake Victoria, Uganda, to determine the potential impact of alcohol interventions on HIV risk.

Methods: In a community-based cohort study conducted among participants aged 18-49 years, data on risk behaviours including alcohol consumption and its frequency, were collected at baseline and 12 months follow-up visits. Venous blood samples were collected for HIV serological testing. HIV incidence rates and adjusted incident rate ratios (Adj. IRR) were estimated by Poisson regression models. Crude and adjusted PAFs of incident HIV infections associated with alcohol consumption were calculated as [1-Pr(HIV incident infection given no alcohol consumption)/ Pr(HIV incident infection)] x100, using the Greenland and Drescher method for cohort studies and Stata *punaf* command.

Results: Overall, 48 incident HIV infections occurred giving a cumulative incidence of 3.72% (95% CI, 2.74 - 4.94) and an incidence rate of 3.39/100 pyar (95% CI, 2.55 - 4.49). Of these, 10 (20.8%) occurred among none alcohol drinkers, 12 (25.0%) in occasional drinkers and 26 (54.2%) in regular drinkers (trend $p<0.0001$). Having 2+ total sexual partners, 2+ new sexual partners, and alcohol drinking before sex were highest among regular alcohol drinkers, followed by occasional drinkers, and least among none drinkers (all trend p values <0.0001). The overall crude and adjusted PAFs were 55.8% (95% CI; 23.3 - 74.6) and 63.8% (95% CI; 23.8 - 82.8) respectively. The lowest adjusted PAF of 52.4% (95% CI; 12.4 - 74.1) was observed among Moslems who drink alcohol while the highest of 70.8% (95% CI; 33.0 - 87.3) occurred among participants who reported 2+ sexual partner in the past 12 months.

Conclusions: In fishing communities along Lake Victoria, Uganda, alcohol is associated with high risk behaviours and 64% of all new HIV infections are associated with alcohol consumption. It might be important to integrate interventions for reducing alcohol consumption in HIV/AIDS control packages.

1039 Risky Sexual Behavior and HIV Infection Among Fisher Folk: Lake Kyoga Region, Uganda

Rose Apondi[1]; Rhoda Wanyenze[2]; Herbert S. Kiyingi[2]; Abdu-Maliki Muyinda[2]; Elizabeth Meassick[1]; Joy Kusiima[2]; David Serwadda[2]
[1]CDC Center for Global Health, Division of Global AIDS/HIV, Kampala, Uganda; [2]Makerere University School of Public Health, Kampala, Uganda

Background: Several studies in Sub-Saharan Africa have documented higher HIV infection rates in fishing communities than the general population. An understanding of the specific sexual behavior associated with increased HIV infection risk in fishing communities is critical to the design of effective prevention interventions. This study assessed risky sexual behavior and its association with HIV infection among fishing communities around the Lake Kyoga region in Uganda.

Methods: A two stage sampling design was used in a cross-sectional survey to obtain blood, urine and stool samples to determine HIV-1 status for 1786 individuals. The survey collected quantitative and qualitative data on HIV knowledge, sexual behavior and access to health services. Risky sexual behavior was defined as report of transactional sex and or report of sex with multiple sexual partners coupled with non- consistent condom-use. Using univariate and bivariate analysis, socio-demographic factors associated with risky sexual behavior and HIV infection were identified including alcohol and drug use.

Results: This fishing community presents an HIV prevalence rate of 14.3%, which is twice the national general population HIV rate. The HIV prevalence rate for this region is much lower than the rate reported in the Lake Victoria region ranging from 22% to 40%. There was no difference in rates of condom use between the HIV infected or uninfected respondents (Unadjusted OR: 1.3 [0.78 – 2.00]), p-value <0.35). This was also true of HIV infected individuals who engaged in transactional sex. We found no difference in risky behavior between the men and women (Unadjusted OR: 1.0 (0.88 – 1.16). HIV infection rates were highest among those who were divorced or separated. The odds of being HIV positive among individuals who reported ever swallowing, sniffing, smoking, or injecting drugs were higher than for individuals who did not (Unadjusted OR 1.90 [1.09 – 3.33]).

Conclusions: This study offers evidence on risky behavior and HIV infection contrary to data from other fishing communities. HIV infected individuals in this population reported protected sex which may explain the lower population HIV prevalence rates. Longitudinal studies on risky behavior for HIV-infection would be important to maximize public health benefits among fishing communities as treatment for prevention rolls out.

THURSDAY, FEBRUARY 26, 2015

Session P-W5 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Incidence and Prevalence of HIV Infection, Including Acute HIV

1040 Increases in HIV Diagnoses Among MSM in Metropolitan Statistical Areas, United States, 2003–2012

Lorena Espinoza; H. Irene Hall; Tian Tang; Anna Satcher Johnson; Amy Lansky
US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: Monitoring trends in HIV diagnosis by metropolitan statistical area (MSA) provides public health programs with data to develop and evaluate more effective prevention strategies and to set priorities for resource allocation.

Methods: Using data from the National HIV Surveillance System (NHSS) reported through December 2013, we assessed trends in HIV diagnoses in MSAs in the United States and Puerto Rico. We determined the annual numbers and rates (per 100,000 population) of HIV diagnoses during 2003–2012 among persons aged ≥13 years. MSAs were defined as population ≥500,000. Poisson regression was used to calculate the estimated annual percent change (EAPC) in annual rates or numbers. MSAs with case counts < 12 were excluded from EAPC calculations. Data were adjusted for missing information on risk factors. Because of a non-monotone trend in HIV diagnoses among men who have sex with men (MSM), we report on diagnoses during 2008-2012 (adjusted for reporting delays).

Results: During 2003–2012, the overall annual rate of HIV diagnoses in MSAs decreased 3.9% per year (95% confidence interval [CI] = –4.0,–3.7). Significant decreases were observed in 64% of the 105 MSAs. Annual rates in MSAs decreased overall (–2.9%; 95% CI= –3.0,–2.8) among males (54% of individual MSAs) and (–6.9%; 95% CI= –7.1,–6.7) among females (68% of individual MSAs). Rates decreased among blacks overall (–4.2%; 95% CI= –4.4, –4.0) and in 42% of individual MSAs, Hispanics/Latinos (–4.9%; 95% CI= –5.1, –4.7; 59% of individual MSAs) and whites (–3.8%; 95% CI= –4.0, –3.6; 47% of individual MSAs). However, rates increased in 5 MSAs among blacks and in 2 MSAs among whites. The number of diagnoses among MSM increased from 2003 to 2007 (relative percent increase, 10.8%) and then decreased (-4.1%). However, in the later period diagnoses among MSM significantly decreased only in 4 MSAs and increased in 9 MSAs. In 59 MSAs with >12 annual diagnoses among MSM 13-24 years, diagnoses increased in 19 MSAs among these young MSM.

Conclusions: Increases in HIV diagnoses were observed in particular MSAs among MSM, blacks and whites. The geographic disparity in HIV burden indicates a need to target prevention

1041 Disparities in HIV by Race and Age Among Men Who Have Sex With Men, 20 US Cities

Cyprian Wejnert; Kristen Hess; Chuck E. Rose; **Alexandra B. Balaji**; Justin C. Smith; Gabriela Paz-Bailey
On behalf of the NHBS Study Group
US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: We evaluated disparities by age and race in HIV prevalence, awareness of infection, and risk behaviors among men who have sex with men (MSM) in 2011 and changes in disparities in HIV prevalence between black and white MSM from 2008 to 2011. Black MSM are disproportionately affected by HIV. According to CDC, 45% of the estimated new infections in 2010 among black MSM occurred among those younger than 25 years old.

Methods: We examined National HIV Behavioral Surveillance (NHBS) data among MSM from 20 U.S. cities in 2008 and 2011. Time-location sampling was used to recruit men for interview and HIV testing. We analyzed data for men who reported ≥1 male sex partner in the past 12 months and had a valid HIV test result. Using 2011 data, we used Poisson models with robust error variances to test racial/ethnic disparities by age in HIV prevalence, HIV awareness, past 12 months condomless anal sex (CAS), and CAS with a partner of discordant or unknown HIV status at last sex. Finally, we use a Poisson model to compare changes in racial/ethnic disparities in HIV prevalence between 2008 and 2011.

Results: Among 2216 black MSM tested in 2011, 665 (30%) were HIV infected; among 802 young black MSM aged 18-24 years tested in 2011, 167 (20%) were HIV infected. In all age groups younger than 40 years, black MSM were significantly more likely to be HIV infected than all other racial/ethnic groups analyzed. HIV-infected black MSM were less

likely to be aware of their infection than their white counterparts (p<0.001). Black MSM did not report higher percentages of CAS in the past 12 months or CAS with a partner of discordant or unknown HIV status at last sex. The disparity in HIV prevalence between black and white MSM increased between 2008 and 2011 (p=0.014).

Conclusions: Our findings show racial disparities in HIV infection among MSM are especially large among young MSM. These findings show that black MSM are being infected with HIV at younger ages compared to MSM of other racial/ethnic groups. In our data, 1 in 5 black MSM aged 18-24 were infected with HIV. Black MSM were most likely to be infected with HIV and least likely to be aware of their infection, but did not report higher levels of sexual risk behavior than other MSM. Further, racial disparities in HIV prevalence between black and white MSM increased from 2008 to 2011. Prevention efforts focused on black MSM may maximize their impact by addressing the prevention needs of black MSM younger than 25 years old.

1042 HIV Incidence Estimates, Introducing the Limiting Antigen Avidity EIA to Existing HIV Surveillance in Kiev City, Ukraine: 2013–2014

Ruth Simmons[1]; Ruslan Malyuta[2]; Nelli Chentsova[3]; Iryna Karnets[3]; Gary Murphy[4]; Antonia Medoeva[3]; Yuri Kruglov[5]; Alexander Yurchenko[3]; Kholoud Porter[1]; Andrew Copas[1]

[1]Medical Research Council at University College London, London, United Kingdom; [2]Perinatal Prevention of AIDS Initiative, Odessa, Ukraine; [3]Kyiv City AIDS Centre, Kyiv City, Ukraine; [4]Public Health England, London, United Kingdom; [5]Institute of Epidemiology, Kyiv, Ukraine

Background: Little is known about HIV incidence in Ukraine which is important for an accurate picture of those at greatest risk of HIV. Serological methods to differentiate recent from non-recent HIV infections were introduced to routine surveillance in Kiev City, to estimate incidence and to characterise those newly-diagnosed and infected.

Methods: Using existing testing services within Kiev City, residual samples from persons newly diagnosed with HIV were tested to differentiate a recent from non-recent infection using an avidity assay. All persons (≥16yrs) presenting for an HIV test April 2013 - March 2014 were included and demographic data on possible risk factors for HIV acquisition, and testing history were added to the existing data collection. Incidence rates were estimated using an extrapolation method published by Prejean et al.

Results: During the study period 6370 individuals tested for HIV. Of these, 467 (7.8%) were HIV positive, equivalent to a diagnosis rate of 21.5 per 100,000 population. The highest prevalence was among 31-35 year olds (11.2%), males (9.4%), people who inject drugs (PWID) (17.9%) and men who have sex with men (MSM) (24.1%). Incidence estimates for Kiev City were 21.5 per 100,000 (18.2-26.1), with 6.5% classified as recent. The disproportionate distribution of HIV among MSM and PWID was evident. Adjusting for all variables in a multivariate model the only independent predictor for being recently infected was HIV risk group, with MSM more likely to test recent compared with heterosexual contact. We estimate incidence to be between 2289.6 and 6868.7 per 100,000 for MSM and 350.4 for PWID in Kiev City.

Conclusions: This is the first estimate of HIV incidence in Ukraine and should enable targeted public health action and health promotion work to be made, laying the foundation for local and national guidelines.

1043 Detection of Acute HIV Infection, US National HIV Surveillance System, 2008–2012

Laurie Linley; Qian An; Kristen Mahle Gray; Alexandra Oster; Angela L. Hernandez

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: Detection of acute HIV infection (AHI) is critical to delay disease progression and reduce the spread of HIV. In June 2011, an updated laboratory HIV diagnostic testing algorithm that facilitates detecting acute HIV was included in the revised laboratory-based HIV testing guidelines issued by the Clinical and Laboratory Standards Institute (CLSI). We used laboratory and testing history data collected as part of the U.S. National HIV Surveillance System (NHSS) to identify persons with AHI, assess potential shifts from recent changes in HIV testing technology, and describe populations newly acquiring and transmitting HIV.

Methods: We analyzed NHSS data for persons aged ≥13 years with HIV diagnosed during 2008-2012 who had a date of most recent HIV antibody-negative test either through a laboratory test result or patient/provider report. Those with a negative test ≤60 days before HIV diagnosis were considered AHI. We compared persons with AHI to all persons diagnosed with HIV by demographic, risk, and geographic characteristics, and CD4 and viral load (VL) data measured within 3 months after diagnosis.

Results: Of 219,773 HIV-diagnosed persons, 56,944 (25.9%) had a previous negative test date, of whom 1,791 (3.1%) met criteria for AHI. Although the percentage of diagnoses categorized as AHI was relatively stable during 2008-2011, there was a significant increase from 3.2% in 2011 to 3.6% in 2012 (p<0.05). Compared with all HIV-diagnosed persons, significantly higher percentages (p<0.0001) of persons with AHI were white or Hispanic/Latino, aged 13-29 years, men who have sex with men, and from the Western or Northeastern regions of the United States [Table]. Compared with all HIV-diagnosed persons with CD4 or VL results within 3 months of diagnosis, a significantly higher percentage of those with AHI had a CD4 result >350 (72.7% vs. 44.8%, p<0.0001) or VL >1,000,000 copies/μl (14.3% vs. 8.9%, p<0.0001).

Number and Demographic Distribution of Persons with Acute HIV Infections Compared with All HIV-Diagnosed Persons, National HIV Surveillance System, 2008-2012

		No. Acute HIV Infections (%)	No. HIV-Diagnosed (%)	p-value
Race/ethnicity	Black/African American	731 (40.8)	102,796 (46.8)	<0.0001
	Hispanic/Latino	408 (22.8)	45,185 (20.6)	0.02
	White	559 (31.2)	60,543 (27.5)	<0.001
	Other	93 (5.2)	11,249 (5.1)	0.89
Age group (years)	13-29	993 (55.4)	77,127 (35.1)	<0.0001
	30-39	415 (23.2)	53,453 (24.3)	0.26
	40-49	266 (14.9)	51,991 (23.7)	<0.0001
	50+	117 (6.5)	37,202 (16.9)	<0.0001
Transmission category	MSM	1,246 (69.6)	108,367 (49.3)	<0.0001
	IDU	67 (3.7)	10,774 (4.9)	0.02
	MSM/IDU	65 (3.6)	5,687 (2.6)	<0.01
	Heterosexual contact	194 (10.8)	37,675 (17.1)	<0.0001
	Other/Unknown	219 (12.2)	57,270 (26.1)	<0.0001
Region	Northeast	466 (26.0)	42,338 (19.3)	<0.0001
	Midwest	145 (8.1)	27,849 (12.7)	<0.0001
	South	627 (35.0)	110,197 (50.1)	<0.0001
	West	553 (30.9)	39,389 (17.9)	<0.0001

MSM: male-to-male sexual contact; IDU: injection drug use

Conclusions: NHSS data indicate demographic and geographic disparities in the detection of AHI among HIV-diagnosed persons. The increase in AHI in 2012 may suggest a potential shift in testing technology and reporting to public health following the revised CLSI guidelines. Widespread implementation of CDC's updated recommendations for laboratory HIV testing released in June 2014 will enhance the detection of acute HIV infection and optimize opportunities for treatment and prevention.

1044 Differences in Acute Retroviral Syndrome by HIV-1 Subtype in a Multicentre Cohort Study in Africa

Eduard J. Sanders[1]; Kimberly A. Powers[2]; Etienne Karita[3]; Anatoli Kamali[4]; William Kilembe[5]; Susan Allen[6]; Eric Hunter[6]; Omu Anzala[7]; Pat Fast[8]; Matthew Price[8]

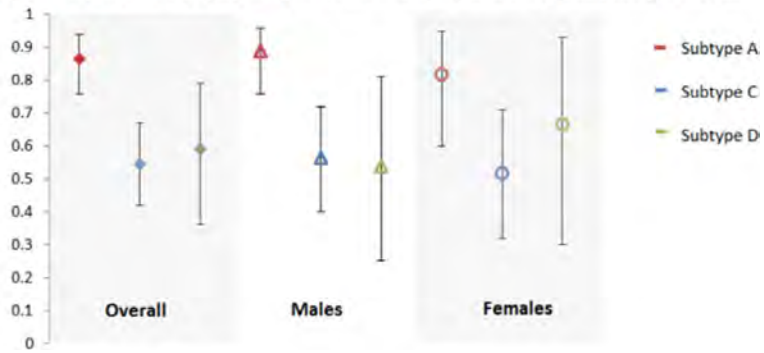
[1]KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya; [2]University of North Carolina, Chapel Hill, NC, US; [3]Project San Francisco, Kigali, Rwanda; [4]Medical Research Council/Uganda Virus Research Institute, Entebbe, Uganda; [5]Zambia Emory Research Project, Lusaka, Zambia; [6]Emory University, Atlanta, GA, US; [7]Kenya AIDS Vaccine Initiative, Nairobi, Kenya; [8]International AIDS Vaccine Initiative,, New York, NY, US

Background: Symptoms of acute retroviral syndrome (ARS) in African adults differ by region and timing of ascertainment, with two Kenyan cohort studies that followed subjects monthly showing a higher report of symptoms and signs than a cohort study from Zambia that followed subjects every 3 months. We sought to determine whether reporting of ARS was associated with HIV-1 subtype at nine participating African research centres (CRC), representing countries with predominant HIV-1 subtypes A, C and D.

Methods: Adults with acute or early HIV-1 infection in a multicenter HIV-1 incidence study were enrolled in a sub-study assessing ARS. Estimated date of infection (EDI) was based on a positive plasma viral load or p24 antigen test prior to seroconversion, or the mid-point between a negative and positive HIV-1 serologic test. Eleven ARS signs and symptoms were assessed at sub-study enrollment. We used log-binomial regression to estimate the prevalence of ARS signs and symptoms ascertained in the period ≤ 42 days after EDI, by subtype, and sex.

Results: Among 155 volunteers ascertained within 6 weeks following EDI, 67 (43.2%) had pol-derived subtype A, 66 (42.6%) subtype C, and 22 (14.2%) subtype D infection. The number of men and gender ratio by subtype for subtype A was 45 (67%) men; for subtype C: 39 (59%) men, and for subtype D: 13 (59%) men. Individuals with subtype A were statistically significantly more likely than individuals with subtypes C and D to report any of the specifically-listed ARS symptoms, and among those reporting any symptoms (figure), the mean number of symptoms was significantly greater among those with subtype A than among those with subtype C or D. These associations were not modified by sex.

Figure: Proportion (95% CI) reporting any of the listed symptoms and signs, by subtype and sex:



Conclusions: In this multicenter African cohort of patients evaluated within 6 weeks following EDI, individuals with subtype A were significantly more likely than individuals with subtypes C and D to report any of the 11 specifically-listed ARS symptoms. Further studies elucidating differences in innate immune responses by HIV-1 subtype in patients with acute HIV infections are recommended.

1045 Using GPS Data to Construct a Spatial Map of the HIV Epidemic in Malawi

Danielle E. Robbins; Brian J. Coburn; Sally Blower

David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US

Background: In order to develop effective control strategies for HIV epidemics, it is essential to know how many individuals are infected with HIV and their location; i.e. to construct a density of infection (DoI) map. Here we show how to construct such a map for Malawi where the prevalence of HIV is ~11%.

Methods: We used geo-referenced data from the 2010 Malawi Demographic and Health Survey (MDHS), a nationally representative survey that included HIV testing. An individual's demographic characteristics are linked with their test results. We used data from 7,091 women and 6,497 men aged 15-49 years old. We used these geo-referenced data and applied spatial interpolation techniques to construct a surface prevalence map of the HIV epidemic for the entire country. We then used WorldPop data to construct a demographic map showing the geographic distribution of the population and the population density. We then constructed the DoI map for Malawi by combining the surface prevalence and demographic maps using raster multiplication.

Results: The surface prevalence maps shows that there is significant geographic variation in HIV prevalence throughout the country. In the rural northern region prevalence is ~7%. In the central region, which is semi-urban (i.e. a mix of rural and urban) prevalence is only slightly higher, ~8%. Notably, HIV prevalence is substantially higher (~15%) in the southern urban region. In all regions prevalence is higher in women than in men: ~8% vs. ~5% (northern region), ~9% vs. ~6% (central region), and ~18% vs. ~11% .The demographic map shows that there is significant spatial clustering of the population: 10% of the country contains 48% of the population. In addition 13% of the population lives in the northern region, 42% lives in the central region, and 45% in the southern region. Overall, over 60% of the population lives in urban centers. Our DoI map shows that although the HIV epidemic in Malawi is generalized, the majority of the infected individuals live in urban centers. Using our map we estimate that approximately 690,000 individuals aged 15-49 are infected.

Conclusions: The new methodology that we have developed enables us to identify, and locate, both diagnosed and undiagnosed individuals who are infected with HIV. The DoI maps can be used to identify the areas in greatest need of treatment and prevention programs. Notably, the methodology that we have developed can be used to construct DoI maps for 23 other sub-Saharan African countries.

1046 HIV Incidence in Rural Malawi During Widespread Antiretroviral Treatment Availability

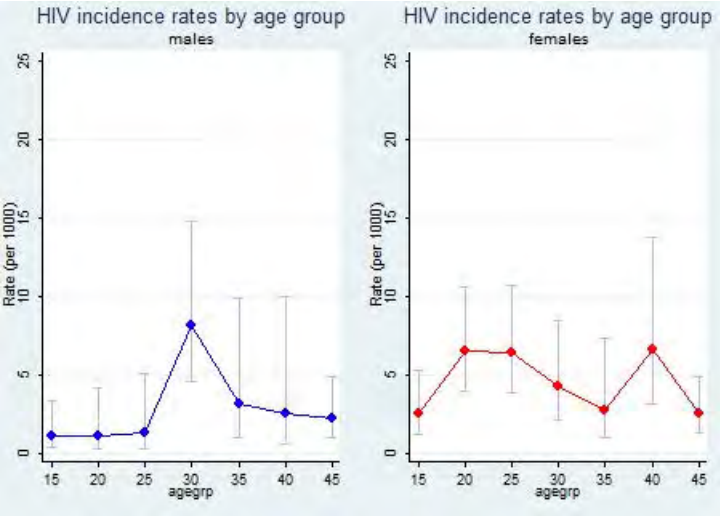
Alison Price[1]; Menard Chihana[2]; Ndoliwe Kayuni[2]; Amelia C. Crampin[1]; Milly Marston[1]; Basia Zaba[1]; Estelle McLean[1]; Olivier Koole[1]; Moffat Nyirenda[1]

[1]London School of Hygiene and Tropical Medicine, Chilumba, Malawi; [2]Karonga Prevention Study, Chilumba, Malawi

Background: In Malawi adult mortality and death attributable to HIV has fallen with widespread availability of antiretroviral treatment (ART) since 2005 and HIV prevalence approaches 8%. However the population impact on HIV incidence in this period is unclear.

Methods: We used population-level demographic surveillance and annual socioeconomic and HIV sero-survey data from Karonga Prevention Study in rural Malawi, collected between 2007 and 2011, to calculate age specific incidence rates and rate ratios (using Poisson regression), by calendar year and socio-demographic factors, with adjustment for potential confounders.

Results: During four years of follow up there were 97 new HIV infections (3.4 per 1000 person years (pyrs); 30 men and 67 women). The HIV incidence was 2.4 (95% CI 1.6 – 3.4 per 1000 pyrs) and 4.3 (95%CI 3.3 – 5.4 per 1000 pyrs) in men and women, respectively. Age specific rates are shown in Figure 1. HIV incidence rates did not differ materially across surveys (p trend >0.05). The association with marital status varied by sex (p heterogeneity <0.05) with never married women and polygynously married men at increased risk for HIV infection compared with monogamously married individuals of the same sex (hazard ratio (HR) for never married women 5.5; 95% CI 2.3 -13.2 and HR for polygynous men 1.8; 95% CI 1.0 - 9.6). Roadside living was associated with a higher HIV incidence than rural residence (4.7 per 1000 pyrs vs. 2.0 per 1000 pyrs: HR 2.6; 95%CI 1.6 – 4.1). Education level was not associated with risk for HIV infection (p>0.05).



Conclusions: In this rural population, rates of new infection are low and did not vary materially during 2007 to 2011 despite increasing availability of ART although risk for infection varied by age, location of residence and marital status.

1047 HIV-1 Incidence Among Adult STI Clinic Patients in Blantyre, Malawi

Fatima Zulu[1]; Isaac Singini[1]; Newton I. Kumwenda[1]; Johnstone Kumwenda[1]; Sufia Dadabhai[2]

[1]Johns Hopkins University Research Project, Blantyre, Malawi; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

Background: Measuring HIV incidence is the gold standard for determining the stage of the country's epidemic. There are limited incidence data from Malawi, where national adult HIV prevalence ia 10.6%. We conducted a study to measure incidence of HIV and associated risk factors in patients seeking sexually transmitted infection (STI) screening and care at Queen Elizabeth Central Hospital in Blantyre, Malawi.

Methods: We conducted a prospective cohort study among adults, presenting at the STI clinic at the main public referral hospital in Blantyre. Between August 2010 and December 2012, all patients presenting at the clinic were counseled and tested for HIV using HIV rapid tests. HIV negative individuals were consented for enrollment. A blood sample was collected for HIV RNA PCR testing to determine Acute HIV Infection. We collected demographics, sexual behavior, and medical history. Participants were followed-up every 3 months for 18 months or until seroconversion confirmed by Western Blot. HIV incidence was calculated by dividing total number of new infections by total observed person-years (PY); 95% confidence intervals (CI) were calculated. Incidence rates were compared using the Chi-square test for categorical variables and t-test for continuous variables. Adjusted relative risks were used to identify significant risk factors for HIV seroconversion.

Results: We screened 3335 patients,1045 enrolled. Mean age was 28.2 years (range 18-52) among women and 27.9 years (range 18-59) among men. Overall HIV incidence was 3.9/100PY [95% CI 3.1 - 4.9]. Incidence among participants aged ≤25 years was 4.1/100PY [95% CI 2.8-5.8] compared to 3.8/100PY [95% CI 2.8-5.1] among those aged >25 years (p-value 0.16). Across age groups, HIV incidence rate was significantly higher among men (4.9/100PY 95% CI 3.7-6.4) compared to women (2.6/100PY, 95% CI 1.7 - 3.9, p-value 0.001), with the exception of young women (≤20 years) who had an incidence rate of 4.7/100PY (95%CI 3.1-7.3) compared to young men 3.1 (95% CI 1.6 - 5.9). Genital ulcerative disease (GUD) (RR=3.78, 95% CI 2.0, 7.18) and history of STI (RR=2.1 95% CI 1.6 -4.7) were independently associated with HIV seroconversion.

Conclusions: We found high HIV incidence among adults seeking STI care in Blantyre but lower than previously reported (3.4). These results suggest the comprehensive national response to HIV may be curbing new infections. Specific vulnerable populations still require targeted prevention services.

THURSDAY, FEBRUARY 26, 2015

Session P-W6 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Disease Progression, Morbidity, and Mortality

1048 CD4 Cell Dynamics in HIV-1 Infection Before and After ART: Overview and Determinants

Anne Cori[1]; Mike Pickles[1]; Ard van Sighem[2]; Luuk Gras[2]; Daniela Bezemer[2]; Peter Reiss[2]; Christophe Fraser[1]
On behalf of the ATHENA Observational Cohort

[1]Imperial College London, London, United Kingdom; [2]HIV Monitoring Foundation, Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands

Background: CD4 cell count is a key measure of HIV disease progression, and has been the basis of successive international guidelines for treatment initiation. CD4 cell dynamics are used in mathematical and econometric models for evaluating public health needs and interventions.

Methods: Here, we analyse a subset of the ATHENA cohort, including individuals with date of infection estimated to within one year and with extensive and intensive clinical follow up. Because CD4 counts are intrinsically noisy, we separate the analysis of individual CD4 dynamics over time into a model of long-term trends of smoothed CD4 counts, and an observation model that relates actual CD4 measurements to the underlying smoothed counts. We use a monotonic spline smoothing model, and based on smoothed counts derive the average time to CD4 thresholds CD4≤500, CD4≤350, CD4≤200 cells/mm^3 as well as the average time to death, and the proportion of individuals starting in each category after seroconversion. We examine individual-level co-factors which influence these rates. We perform the analysis in both newly infected individuals that have not received antiretroviral therapy (ART) and those who have interrupted therapy for at least six months.

Results: Amongst untreated individuals, the time spent in each compartment was on average 3.09 (CD4>500 cells/mm^3), 2.49 (CD4 350-500), 4.95 (CD4 200-350) and 1.07 (CD4≤200) years. Only 77% of individuals had CD4 >500 cells/mm^3 at or shortly after seroconversion. Set-point viral load (SPVL) was an important determinant of CD4 progression; individuals with ≥5 log10 copies/ml took 5.32 years to reach CD4≤200 cells/mm^3 compared to 11.53 years for SPVL <4 log10 copies/ml (see table). SPVL was not an important predictor of progression after treatment interruption, and CD4 dynamics were otherwise similar to pre-ART dynamics, providing evidence of true immune reconstitution during ART.

	From infection	From CD4 >500	From CD4 350-500	From CD4 200-350
logSPVL < 4.0	11.53 (9.39-13.18)	12.26 (10.06-13.90)	7.46 (5.47-9.10)	4.49 (2.72-6.07)
logSPVL 4.0-4.5	10.19 (7.60-11.63)	10.95 (8.34-12.47)	7.89 (5.35-9.36)	5.23 (2.84-6.64)
logSPVL 4.5-5.0	7.94 (6.19- 9.07)	8.69 (6.88- 9.92)	6.44 (4.72-7.59)	4.23 (2.56-5.38)
logSPVL > 5.0	5.32 (3.96- 6.34)	5.80 (4.36- 6.82)	4.44 (3.08-5.55)	2.98 (1.66-4.04)

Estimated average time (in years) to reaching CD4 200 cells/mm3, given current stage of infection, stratified by set point viral load (SPVL): mean estimate (95% confidence interval)

Conclusions: Our analyses show that many individuals already have CD4≤500 cells/mm^3 at or shortly after seroconversion, and that set point viral load strongly influences initial CD4 cell count as well as rate of CD4 decline. Hence guidelines on treatment initiation should consider criteria based on both current CD4 count and viral load., while mathematical models should incorporate SPVL stratification. Our study also provides new estimates of CD4 dynamics after interruption of ART, which could be used in such models.

1049 IL-6 Partially Mediates the Effect of HIV Status on Survival

Kaku So-Armah[1]; Amy Justice[2]; David Rimland[3]; Maria Rodriguez-Barradas[4]; Adeel A. Butt[5]; David Leaf[6]; Russell Tracy[7]; Mohammad Sajadi[8]; Cynthia Gibert[9]; Matthew S. Freiberg[10]

[1]Yale University School of Medicine, New Haven, CT, US; [2]VA Connecticut Healthcare System, West Haven, CT, US; [3]Veterans Affairs Medical Center, Atlanta, GA, US; [4]Veterans Affairs Medical Center, Houston, TX, US; [5]Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates; [6]Veterans Affairs Medical Center, Greater Los Angeles, CA, US; [7]University of Vermont, Burlington, VT, US; [8]Veterans Affairs Medical Center, Baltimore, MD, US; [9]Veterans Affairs Medical Center, Washington, DC, US; [10]Vanderbilt University School of Medicine, Nashville, TN, US

Background: Biomarkers of inflammation (e.g. interleukin 6 (IL-6)) have been associated with mortality separately in HIV infected (HIV+) and uninfected cohorts. It is unclear whether inflammation as measured by IL-6 mediates and/or moderates the association between HIV status (infected and uninfected in same cohort) and mortality.

Methods: Methods: Serum IL-6 was obtained from 1491 HIV+ and 820 uninfected participants from the Veterans Aging Cohort Study at baseline (2005-2007). Participants were followed until death or 7/25/2013. IL-6 values were compared using median regression. Cox models were used to assess mediation (Baron and Kenny) and moderation (interaction of HIV and IL-6).

Results: Over a median of 6.9 (mean 6.4) years, 410 deaths occurred (15% of uninfected group, 19% of HIV+ group). HIV+ participants were younger, less likely to be female, had less prevalent cardiovascular disease, hypertension, diabetes, BMI>30 kg/m^2, and more current hazardous alcohol consumption, and hepatitis C at baseline. Median [IQR] IL-6 level was higher among HIV+ versus uninfected people (2.1 [2.0] vs. 1.8 [2.1] pg/mL). Levels were particularly high among those with HIV-1 RNA between 500-10000 and ≥10000 copies/mL (2.0 [1.9] and 2.6 [2.8] pg/mL; p<0.05 for all comparisons to uninfected groups after confounder adjustment). Compared to uninfected people, HIV infected people with ongoing viral replication had increased mortality risk (Table 1). This association persisted after adjusting for confounders (Table 1). Further adjustment for IL-6 quartiles attenuated the association of HIV with mortality at higher HIV-1 RNA levels suggesting mediation is present (Table 1). There was a strong, stepwise increasing association of IL-6 quartiles with mortality (Table 1). This association was independent of HIV status. No statistically significant interactions were observed between HIV (stratified by HIV-1 RNA) and IL-6 quartiles in Cox models (p>0.05 for global tests of interactions).

Table 1: Hazard Ratio (95% confidence interval) for association between HIV and interleukin-6 (IL-6) and mortality

	Model 1A	Model 1B	Model 2A	Model 2B
HIV status (HIV-1 RNA/ copies per mL)	**Age, race-ethnicity adjusted**	**Age, race-ethnicity + IL-6 adjusted**	**Fully adjusted***	**Fully adjusted + IL-6 adjusted***
HIV uninfected	1.0 (REF)	1.0 (REF)	1.0 (REF)	1.0 (REF)
HIV+ (<500)	1.09 (0.86-1.39)	1.10 (0.86-1.4)	1.12 (0.86-1.46)	1.07 (0.82-1.39)
HIV+ (500-9999)	1.59 (1.12-2.26)	1.56 (1.1-2.22)	1.56 (1.08-2.25)	1.52 (1.05-2.19)
HIV+ (≥10,000)	2.93 (2.2-3.89)	2.44 (1.83-3.26)	2.81 (2.08-3.8)	2.35 (1.72-3.19)
IL-6 quartile (range/pg/ml)				
(<1.7)		1.0 (REF)`		1.0 (REF)
(1.7-2.9)		1.4 (1.06-1.85)		1.26 (0.94-1.67)
(2.9-5.1)		2.1 (1.59-2.78)		1.72 (1.29-2.3)
(>5.1)		3.76 (2.84-4.99)		3.08 (2.30-4.13)

*Adjusted for age, race-ethnicity and prevalent cardiovascular disease, cancer, diabetes, chronic obstructive pulmonary disease, hypertension, smoking, hepatitis C, obesity, hypercholesterolemia, alcohol, cocaine use and IL-6 quartiles (thresholds defined among those who died).

Conclusions: HIV infection with ongoing viral replication and elevated IL-6 were significantly and independently associated with mortality. To the degree that IL-6 captures effects of inflammation, our results support the conclusion that inflammation is an underlying mechanism for excess risk of mortality among HIV-infected people with ongoing viral replication compared to uninfected people.

1050 Persistently Elevated Macrophage Activation in HIV+ Women Reporting Heavy Alcohol Use

Seema N. Desai[1]; Kathleen M. Weber[2]; Jane Burke-Miller[3]; Audrey L. French[2]; Monica Gandhi[4]; Mark H. Kuniholm[5]; Elizabeth T. Golub[6]; Kendall Bryant[7]; Alan Landay[1]; Mardge Cohen[8]

[1]Rush University Medical Center, Chicago, IL, US; [2]CORE Center/Stroger Hospital of Cook County, Chicago, IL, US; [3]Hektoen Institute of Medicine, Chicago, IL, US; [4]University of California San Francisco, San Francisco, CA, US; [5]Albert Einstein College of Medicine, Bronx, NY, US; [6]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [7]National Institutes of Health/National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, US; [8]Stroger Hospital of Cook County, Chicago, IL, US

Background: Alcohol consumption is common in HIV infected women. Heavy alcohol consumption has been associated with accelerated HIV disease progression and poor health outcomes, mainly attributed to inadequate antiretroviral adherence. We hypothesized heavy alcohol consumption alters macrophage activation and inflammation and independently influences HIV disease progression.

Methods: Women's Interagency HIV Study (WIHS) participants who were hepatitis C seronegative were stratified into 4 groups: HIV+ and HIV- with the heaviest chronic alcohol consumption and abstainers, 50/group. Participants were matched on age, race, and education. Soluble macrophage activation marker (sCD163) and sTNF-RII, a marker of inflammation/activation, were measured using ELISA in a subset of n=25/group at 4 time points over 10 years (2001-11). ANOVA was used to examine differences between groups in soluble markers and multivariable random effects logistic and random linear regression models examined associations.

Results: Across the study period, drinkers reported a mean of 21 drinks/week. Adjusting for HAART use, duration and self-reported adherence, HIV+ heavy drinkers (> 7 drinks/week) were more likely to have a CD4 count<350 cells/mm^3 (OR=3.67, p=.005) and detectable viral load (OR=1.65, p=.051) than non-drinkers. sCD163 (mean ng/mL + sd) at baseline was highest in HIV+ drinkers 2098 (1582) compared to HIV+ abstainers 1355 (743), HIV- drinkers 1216 (551), and HIV- abstainers 1349 (673) (F=10.61, p<.001). sTNFRII expression at baseline (mean pg/mL + sd) was higher in both HIV+ drinkers 2692 (889) and HIV+ abstainers 2659 (1093) compared to HIV- drinkers 1697 (557) and HIV- abstainers 1893 (451) (F=4.21, p=.008). Both sCD163 & TNFRII did not significantly change over time. In multivariable longitudinal models, HIV+ drinkers had significantly higher sCD163 than other groups (p<.001); both HIV+ drinkers and HIV+ abstainers had significantly higher sTNFRII than HIV- women (p<.001 and p=.006 respectively). Among HIV+ women, both sCD163 & sTNFRII were significantly associated with elevated viral load (sCD163, p<.001; sTNFRII, p=.021) over time; sTNFRII was associated with lower CD4 cell counts (p=.001).

Conclusions: Chronic heavy drinking is independently associated with HIV outcomes (CD4+ count and viral load). Persistently elevated level of sCD163 in HIV+ve heavy drinkers suggests a mediating role of macrophage activation with implications to persistent inflammation in HIV-infected women reporting heavy alcohol consumption.

1051 Is Survival Following HIV Seroconversion Still Improving, 17 Years After the Introduction of cART?

Ashley Olson[1]; Caroline Sabin[1]; Maria Prins[2]; Laurence Meyer[3]; Julia del Amo[4]; Genevieve Chene[5]; Osamah Hamouda[6]; Giota Touloumi[7]; Kholoud Porter[1]
On behalf of the CASCADE Collaboration in EuroCoord

[1]University College London, London, United Kingdom; [2]Public Health Service of Amsterdam, Amsterdam, Netherlands; [3]Inserm, Paris, France; [4]Instituto de Salud Carlos III, Madrid, Spain; [5]Inserm, Bordeaux, France; [6]Robert Koch Institute, Berlin, Germany; [7]University of Athens, Athens, Greece

Background: Survival of HIV positive individuals has increased since the introduction of cART. We aim to determine if survival and disease free progression in Europe, Australia and Canada are still increasing up to 2013 and to provide updated survival estimates.

Methods: Using CASCADE seroconverter data, we used Cox models to estimate the effect of calendar year on time from HIV seroconversion to death and disease free progression, adjusting for sex, mode of HIV transmission, age at seroconversion (SC), acute infection, and cohort. We investigated if there was interaction between sex, mode of HIV transmission and calendar year.

Results: Of 30344 seroconverters with 234250 person years of follow up, 3190 died and 4126 developed AIDS. 25241 (82%) were male, 19024 (62%) infected through sex between men (MSM), 6725 (22%) sex between men and women (MSW), 3610 (12%) injection drug use (IDU) and 1496 (5%) other or unknown. The hazard ratio (HR) (95% CI) for death, compared to the pre-1997 hazard, decreased over time, falling to 0.44 (0.37, 0.53) in 1997 and reaching 0.08 (0.06, 0.12) in 2013. Similar trends were observed for disease progression with the HR falling to 0.56 (0.49, 0.64) in 1997 and to 0.10 (0.07, 0.14) in 2013. These trends were in parallel with increases in proportion of person time on cART from 17% in 1997 to 72% in 2013. A decreased risk of death was associated with female sex (compared to male sex (HR = 0.79 (0.71, 0.87)), and an increased risk with older age (HR = 1.53 (1.47, 1.59) per 10 year increase) and IDU (2.34, 2.13, 2.57)). We found a significant interaction between sex and mode of HIV transmission with calendar year (p<0.001). Among MSM MSW and other risk groups, HRs of AIDS/death were similar to that of the main analysis for both sexes. However among IDUs HRs of AIDS/death were 0.71 (0.54, 0.94) and 0.73 (0.50, 1.05) in 1997 and 0.29 (0.12, 0.67) and 0.48 (0.19, 1.20) in 2013 for males and females, respectively.

Year	HR (95% CI) of death	HR (95% CI) of AIDS/death	Person time on cART (%)
Pre 1997	1	1	<1
1997	0.44 (0.37, 0.52)	0.56 (0.49, 0.64)	17
1998	0.29 (0.24, 0.35)	0.38 (0.32, 0.44)	33
1999	0.23 (0.19,0.28)	0.34 (0.30, 0.40)	43
2000	0.22 (0.18 ,0.26)	0.32 (0.27, 0.37)	48
2001	0.20 (0.17, 0.24)	0.28 (0.24, 0.32)	49
2002	0.20 (0.17, 0.25)	0.26 (0.22, 0.30)	48
2003	0.18 (0.15, 0.22)	0.28 (0.24, 0.32)	47
2004	0.13 (0.11, 0.16)	0.25 (0.21, 0.29)	47
2005	0.16 (0.14, 0.20)	0.28 (0.24, 0.32)	48
2006	0.13 (0.11, 0.16)	0.22 (0.19, 0.26)	50
2007	0.14 (0.11, 0.16)	0.23 (0.20, 0.26)	52
2008	0.10 (0.08, 0.12)	0.18 (0.15, 0.21)	56
2009	0.09 (0.07, 0.11)	0.17 (0.14, 0.20)	61
2010	0.07 (0.06, 0.09)	0.14 (0.12, 0.17)	66
2011	0.06 (0.04,0.07)	0.16 (0.13, 0.19)	70
2012	0.09 (0.07, 0.12)	0.18 (0.15, 0.22)	70
2013	0.08 (0.06, 0.12)	0.10 (0.07, 0.14)	72

Hazard Ratio (95% CI) for time to death and AIDS/death by calendar year using the CASCADE dataset

Conclusions: Mortality from HIV infection continued to decrease until 2008 and stabilized thereafter. AIDS/mortality continued to decrease over time, stabilizing between 2008-2012 and improving again in 2013. Percent of person time on cART has continued to increase until 2011, stabilizing around 70%.

1052 National Estimates of Life Expectancy After HIV Diagnosis: US HIV Surveillance Data

Azfar-e-Alam Siddiqi; H. Irene Hall; Xiaohong Hu; Ruiguang Song
US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: Previous life expectancy estimates have shown that introduction of highly active antiretroviral therapy has improved the life expectancy after HIV diagnosis, in the United States, from 1996 to 2005. We updated the life expectancy estimates for the years 2008–2011 using surveillance data from all 50 states and DC.

Methods: We used U.S. national HIV surveillance data (adults and adolescents with age at HIV diagnosis ≥13 years) to estimate life expectancy after an HIV diagnosis following the life table approach. Survival within one year, or more than one year after HIV diagnosis was estimated separately and then used to estimate overall life expectancy. Separate sex, race/ethnicity, disease severity (stage 3 vs stages 0–2), and risk factor based average life expectancy estimates were also generated. The data were adjusted for reporting delays and missing risk factors. The differences reported are relative differences of at least 5%.

Results: From year 2008 to 2011, the average life expectancy after HIV diagnosis increased from 25.4 to 28.9 years. Life expectancy was longer for males than for females; improved less for females (females: 23.7–26.4 and males: 26.0–29.6) and showed increasing differences between life expectancies for males and females (2008: 2.3 and 2011: 3.3 years). In 2011, life expectancy for white females was shortest, followed by black females and then Hispanic females. By risk factors, shortest life expectancy was in male injection drug users (IDU), followed by female IDUs and male heterosexuals.

	Estimated life expectancy in years						
		Male			Female		
Year of diagnosis	*Overall*	Black/African American	Hispanic/ Latino	White	Black/African American	Hispanic/ Latino	White
2008	***25.43***	24.08	28.85	25.94	23.02	26.36	24.16
2009	***26.22***	25.39	29.50	26.46	23.54	26.45	25.17
2010	***27.33***	27.31	30.41	27.19	24.51	27.21	24.88
2011	***28.86***	29.46	31.49	28.05	26.25	27.13	26.17

Table 1: Life expectancy of persons diagnosed with HIV, years 2008–2011; overall and by sex and race/ethnicity.

Conclusions: Life expectancy for females of each race/ethnicity group was less than that for males of the same race/ethnicity. Greater disparities in life expectancies by race/ethnicity were seen in males than in females. Disparities in life expectancy by sex and race/ethnicity persist and should be addressed.

1053 Age-Related Morbidities Among HIV-Infected Adults From 2000 to 2010

Cherise Wong[1]; Stephen J. Gange[1]; Michael A. Horberg[2]; Gregory D. Kirk[1]; Anita Rachlis[3]; John Gill[4]; Jennifer E. Thorne[1]; Robert Hogg[5]; James J. Goedert[6]; **Keri N. Althoff**[1]
[1]Johns Hopkins University, Baltimore, MD, US; [2]Mid-Atlantic Permanente Research Institute, Rockville, MD, US; [3]University of Toronto Sunnybrook Research Institute, Toronto, Canada; [4]University of Calgary, Alberta Health Services, Calgary, Canada; [5]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada; [6]National Cancer Institute (NCI), Rockville, MD, US

Background: Among HIV-infected individuals on antiretroviral therapy, conditions typically associated with aging in the general population are emerging as significant sources of concern. Understanding age-related comorbidity occurrence is increasingly important to inform interventions for persons aging with HIV and studies of multimorbidity. The objective of this study was to estimate incidence of hypertension, diabetes, chronic kidney disease (CKD), and anemia in HIV-infected adults in care.

Methods: Data analyzed were from 19 HIV observational cohort studies within the North American AIDS Cohort Collaboration on Research and Design from 2000-2010. The definitions of the 4 morbidities examined were, hypertension: prescription of anti-hypertensive medication, or 2 systolic measures ≥140 mmHg or diastolic measures ≥90 mmHg within 9 months; diabetes: HbgA1c ≥6.5%, or prescription of diabetes-specific medications, or prescription of diabetes-related medications with a history of diabetes diagnosis; CKD: 2 values of eGFR<60 mL/min/1.73 m^2 (per CKD-Epi equation) >90 days apart without an intervening normal value; anemia: 1 measure of hemoglobin<13 g/dL (men) or <12 g/dL (women). Prevalent cases were excluded and participants were required to contribute >1 visit during 2000-2010. Incidence rates (IR) per 100 person-years, adjusted ratios (aIRR) and 95% confidence intervals (95% CI) were estimated using Poisson regression models, adjusted for time-varying age, sex, race, history of injection drug use (IDU), cohort, time-varying CD4 count (<200, 200-349, 350-499, ≥500 cells/mm^3) and time-varying viral load (≤200, >200 copies/mL), and calendar year.

Results: For each outcome, more than 5,000 HIV-infected adults were included in analyses, and contributed a range of 18,494 – 150,662 person-years. There were 6,098 hypertension, 791 diabetes, 1,894 CKD, and 9,039 anemia incident events. Overall, aIRRs showed an increased risk of comorbidity occurrence among older groups, as compared with individuals <40 years of age (Table 1). An increased risk for each comorbidity except diabetes was observed when comparing CD4 counts <200 to CD4 >500.

Table 1. Incident Morbidity Among a Cohort of HIV-Infected Adults in Care in North America From 2000-2010

	Hypertension (n=20,746 people, 63,039 p-years)		Diabetes (n=5,686 people, 18,494 p-years)		Chronic Kidney Disease (n=40,905 people, 150,662 p-years)		Anemia (n=29,439 people, 80,345 p-years)	
IR in Age<40	8.06		2.64		0.42		11.6	
	aIRR*	95%CI	aIRR*	95%CI	aIRR*	95%CI	aIRR*	95%CI
Age (years)								
<40	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref
40-49	1.32	1.25-1.41	1.45	1.17-1.79	2.36	2.01-2.76	0.96	0.92-1.01
50-59	1.81	1.68-1.95	1.75	1.39-2.19	5.79	4.94-6.79	1.16	1.09-1.24
≥60	2.13	1.87-2.43	2.25	1.68-3.01	12.9	10.9-15.5	1.71	1.54-1.89
CD4+ (cells/mm^3)								
≥500	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref
350-499	1.00	0.94-1.08	0.81	0.67-0.98	1.17	1.03-1.34	1.40	1.32-1.49
200-349	1.05	0.98-1.12	0.87	0.72-1.06	1.42	1.25-1.62	2.17	2.05-2.31
<200	1.08	1.00-1.16	0.95	0.76-1.18	2.50	2.20-2.84	4.28	4.03-4.54

IR, incidence rate per 100 person-years; p-years, person-years; aIRR, adjusted incidence rate ratio; CI, confidence interval.
*Poisson regression model adjusted for: age, sex, race/ethnicity, history of IDU, CD4+, viral suppression, cohort, calendar year.

Conclusions: Our data document the occurrence of chronic conditions among HIV-infected adults in North America, particularly among older adults and those with more profound immunosuppression. These findings support the need for comprehensive management and interventions that address complex health needs beyond antiretroviral therapy among aging HIV-infected persons.

1054 A Retrospective Population-Based Examination of Prescription Drug Usage Prior to HIV Diagnosis Among HIV Cases and Their Controls: The Missed Opportunity for Diagnoses Epidemiological Study (MODES)

Souradet Y. Shaw[1]; Laurie Ireland[2]; Tara Carnochan[2]; Nancy Yu[1]; Carla Ens[3]; Yoav Keynan[1]; Ken Kasper[4]; Marissa Becker[1]
On behalf of the MODES Manitoba Team
[1]University of Manitoba, Winnipeg, Canada; [2]Nine Circles Community Health Centre, Winnipeg, Canada; [3]Manitoba Health, Winnipeg, Canada; [4]Manitoba HIV Program, Winnipeg, Canada

Background: In North America, HIV positive individuals continue to present at advanced stages of the disease. Understanding healthcare utilization patterns of HIV positive individuals prior to their diagnosis, such as prescription drug usage, can inform engagement strategies, earlier diagnosis and identification of health care needs.

Methods: This was a population-based, case-control analysis of prescription drug usage of HIV-positive individuals presenting to care between 2007-2011 to the Manitoba HIV program (MHP). HIV cases were age-, sex- and region-matched to their HIV-negative controls at a 1:5 ratio. Clinical information from MHP was linked to the Drug Program Information Network, a real-time database of all drug dispensations in Manitoba. Rates of prescription drug dispensations were calculated for cases and controls. In order to address potential confounding, the total number of pills prescribed, normalized to 7-day dispensation cycles was used as the numerator (as opposed to strictly the number of dispensations). Person-days prior to HIV diagnosis was calculated and used as the denominator in rate calculations. Dispensations were categorized into prescriptions for antibiotics, chronic disease conditions (e.g., asthmas, hypertension) and mental health conditions (e.g., anxiety, bipolar, depression, etc.). Stratified Poisson regression models were used to compare rates between cases and controls. Relative rates (RRs) and their 95% confidence intervals (95%CI) are reported

Results: A total of 164 cases and 809 controls were included. In the year prior to HIV diagnosis, and compared to HIV-negative controls, HIV cases had significantly higher dispensation rates for antibiotics (RR: 3.2, 95%CI: 2.8-3.7), and drugs used to treat diabetes (RR: 1.2, 95%CI: 1.1-1.3), and respiratory conditions (RR: 1.7, 95%CI: 1.4-2.1), while having lower rates for drugs used for hyperlipidemia (RR: 0.7, 95%CI: 0.6-0.8) and hypertension (RR: 0.6, 95%CI: 0.6-0.7). For mental health conditions, HIV cases had significantly higher rates for drugs used to treat anxiety (RR: 2.2, 95%CI: 2.0-2.5), bipolar disorder (RR: 1.4, 95%CI: 1.2-1.7) and mood disorders (RR: 1.1, 95%CI: 1.0-1.2). HIV cases had significantly lower rates for drugs used in the treatment of schizophrenia (RR: 0.7, 95%CI: 0.6-0.8).

Conclusions: With a few exceptions, HIV cases had higher dispensation rates, suggesting both higher co-morbidities and missed opportunities for prevention and care

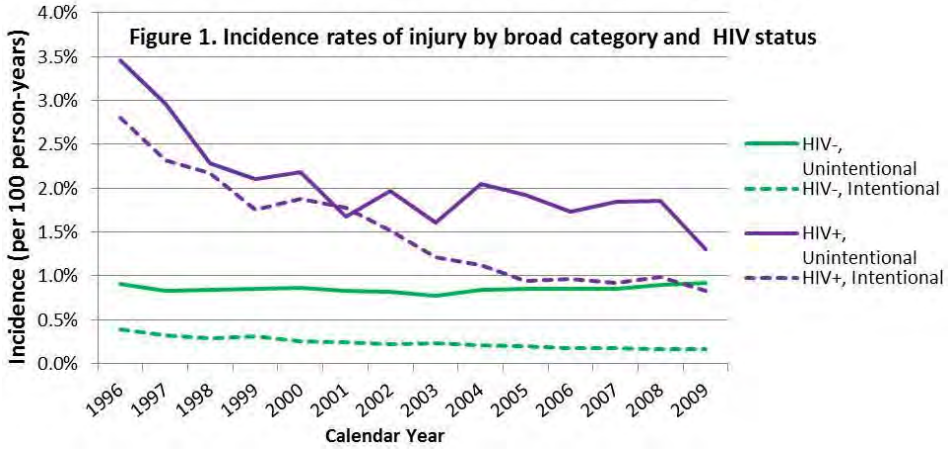
1055 Elevated Rates of Injury Among HIV-Positive Individuals in British Columbia

Hasina Samji[1]; Dmitry Shopin[1]; Wendy Zhang[1]; Oghenowede Eyawo[1]; Guillaume Colley[1]; Mark Hull[1]; Julio Montaner[3]; Robert Hogg[2]
On behalf of the COAST Study
[1]BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; [2]Simon Fraser University, Burnaby, Canada; [3]University of British Columbia, Vancouver, Canada

Background: Injuries are responsible for significant morbidity and mortality, constituting the third leading cause of death and the leading cause of death for those between the ages of 1 and 44 years. The epidemiology of injury in HIV+ individuals has not been well-elucidated. This study seeks to characterize the burden of injuries among HIV+ individuals in comparison to the general population in British Columbia (BC), Canada.

Methods: A population-based dataset was created via linkage between the BC Centre for Excellence in HIV/AIDS and PopulationData^{BC}. Our analytic sample consisted of HIV+ adults in BC identified using validated case-finding algorithms (cohort 1) and a random 1% sample of the adult general population in BC (cohort 2). The International Classification of Diseases 9 and 10 codes were used to classify unintentional (falls, motor vehicle collisions, poisoning, suffocation, fire/burns, natural/environmental, other land transportation and cut/pierce injuries) and intentional (self-harm and assault) injuries based on the external cause of the injury. Incidence rates and 95% confidence intervals were calculated overall for each injury category as well as for sub-categories listed above over the period from 1996 to 2010.

Results: 12,120 (80% male) and 94,373 (50% male) contributed 114,268 and 943,861 person-years (PY) to cohorts 1 and 2, respectively. The incidence of unintentional injury was 18.58/1000PY (95%CI: 17.80-19.39) in cohort 1 and 8.21/1000PY (95%CI: 8.02-8.40) in cohort 2 ($p<0.001$). Rates of intentional injury were 14.69/1000PY (95%CI: 13.97-15.38) and 1.72/1000PY (95% CI: 1.64-1.81), in cohorts 1 and 2, respectively ($p<0.001$). Figure 1 demonstrates a decreasing trend in unintentional and intentional injury among HIV+ individuals over time, while the incidence of injury remains relatively constant in the general population. The highest rates of injury in cohort 1 are associated with self-harm (IR: 8.20, 95%CI: 7.68-8.74), assault (IR: 6.46, 95%CI: 6.01-6.94), and falls (IR: 5.35, 95%CI: 4.93-5.79) (all $p<0.001$ compared to cohort 2).



Conclusions: Elevated rates of intentional and unintentional injury among HIV+ individuals have been identified. While overall rates have decreased over time, disparities in the incidence of unintentional injury in this population remain. Future research will identify risk factors for injury and examine trends by sex, age, and injecting drug use status.

1056 Higher Economic Well-Being Among Virally Suppressed HIV-Infected Adults With CD4>500

Harsha Thirumurthy[1]; Aleksandra Jakubowski[1]; James G. Kahn[2]; Norton Sang[5]; Tamara Clark[2]; Edwin Charlebois[2]; Maya Petersen[3]; Moses R. Kamya[4]; Diane Havlir[2]
SEARCH Collaboration

[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, US; [2]University of California San Francisco, San Francisco, CA, US; [3]University of California Berkeley School of Public Health, Berkeley, CA, US; [4]Makerere University College of Health Sciences, Kampala, Uganda; [5]KEMRI, Kisumu, Kenya

Background: The investment case for HIV treatment as prevention requires consideration of the household economic effects of early initiation of antiretroviral therapy (ART). We examined the association between CD4+ T-cell counts, viral suppression, and economic well-being among HIV-infected adults in 32 rural communities in Kenya and Uganda. We also compared economic outcomes to HIV-uninfected adults in the same communities.

Methods: We conducted socio-economic surveys in households of 100 HIV-infected and 100 HIV-uninfected adults sampled after baseline HIV testing in each of the 32 communities in the SEARCH 'test and treat' study (NCT01864603). CD4+ T-cell counts and HIV RNA were measured for all HIV-infected individuals. Undetectable HIV RNA was defined as <500 copies/mL. Logistic and linear regression models were used to compare employment status, domestic labor, and healthcare utilization between HIV-uninfected adults and HIV-infected adults in different HIV RNA and CD4 strata, adjusting for sociodemographic characteristics and community of residence. Robust standard error estimators were used to account for cluster sampling.

Results: Data were analyzed for 6,608 adults (1,646 HIV-infected, 4,962 HIV-uninfected). After multivariate adjustment, compared to a reference group of HIV-infected adults with CD4≤350 cells/μL, those with CD4>500 and undetectable HIV RNA were significantly more likely to be employed, significantly less likely to lose work due to illness, significantly less likely to spend time receiving healthcare, and significantly less likely to be hospitalized (Table 1). Adults with CD4>500 and undetectable HIV RNA also spent 4.8 fewer hours seeking care in the past month (P<0.01). No significant differences were found between virally suppressed HIV-infected adults with CD4 351-500 and CD4≤350. Finally, outcomes did not differ significantly between virally suppressed HIV-infected adults with CD4>500 and HIV-uninfected adults.

Table 1. Logistic regression results

Outcome	Worked in past week	Lost work due to illness in past month	Spent time receiving care in past month	Spent money on healthcare in past month	Hospitalized in past year
	AOR [95% CI]	AOR [95% CI]	AOR [95% CI]	AOR [95% CI]	AOR [95% CI]
HIV+ CD4≤350	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
HIV+ CD4 351-500, UVL	1.02 [0.74 - 1.42]	0.97 [0.70 - 1.33]	1.06 [0.77 - 1.46]	1.11 [0.81 - 1.52]	0.84 [0.54 - 1.31]
HIV+ CD4>500, UVL	1.59 [1.21 – 2.09]	0.73 [0.57 - 0.95]	0.72 [0.56 - 0.93]	0.80 [0.62 - 1.04]	0.55 [0.39 - 0.79]
HIV–	1.35 [1.12 - 1.63]	0.58 [0.49 - 0.71]	0.53 [0.44 - 0.64]	0.55 [0.45 - 0.66]	0.39 [0.31 - 0.50]

Notes: Results from adjusted logistic regression models with controls for age, education, gender, marital status, wealth, and community.

Abbreviations: UVL, undectable viral load; AOR, adjusted odds ratio

Table 1

Conclusions: HIV-infected adults with higher CD4 counts and undetectable HIV RNA had better economic outcomes and lower healthcare utilization than those with lower CD4 counts, after adjusting for sociodemographic characterstics. The results are consistent with the possibility that ART restores economic outcomes to levels observed prior to a CD4 decline. Ongoing prospective longitudinal evaluation including data on ART usage is needed to rule out alternative explanations and determine whether ART initiation at higher CD4 counts protects economic well-being.

THURSDAY, FEBRUARY 26, 2015

Session P-W7 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HIV Stigma

1057 Internalized Stigma in a Population-Based Sample of US HIV-Infected Adults in Care

Amy R. Baugher; Linda Beer; Jennifer L. Fagan; Christine L. Mattson; Mark Freedman; Jacek Skarbinski

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: Internalized stigma–the extent to which HIV-infected persons hold negative beliefs about HIV as being true about themselves–has been associated with poor HIV medication adherence, non-disclosure of HIV status to sex partners and poor health outcomes. There are no national estimates of the extent of and factors associated with stigma among HIV-infected persons.

Methods: We conducted cross-sectional analyses of data from a nationally representative sample of 4385 HIV-infected U.S. adults receiving medical care who participated in the Medical Monitoring Project in 2011. Stigma was assessed with the Internalized AIDS-Related Stigma Scale (range 0(low)-6(high)). Multivariable linear modeling was conducted to investigate sociodemographic factors that may independently predict mean stigma score. In bivariate analyses, we compared mean stigma scores by behavioral and clinical outcomes using one-way ANOVA ($p<0.05$). Analyses are adjusted for clustering, unequal selection probabilities and non-response.

Results: The overall mean stigma score was 2.6 (standard error=0.04). Characteristics associated with higher stigma scores include: being older, female, black, Hispanic/Latino, heterosexual, foreign born, recently diagnosed (<5 years), homeless; having less than a high school education, having a gap in insurance coverage; and living in poverty. Stigma was independently associated with older age, heterosexual orientation, being foreign born, a gap in insurance coverage and a more recent diagnosis date. In bivariate analysis of outcomes, stigma was related to depression, binge drinking, non-disclosure of HIV status and lower adherence to HIV medicines, but not drug use, sex without a condom in the past 12 months or viral load (Table 1).

Table 1. Bivariate associations between mean internalized stigma score and behavioral and clinical outcomes—United States, 2011 (n=4385)

Characteristic	Weighted mean (95%CL)	Weighted mean of referent group (95%CL)	*p*-value
Major or other depression vs. No depression (ref)	3.3 (3.2-3.5)	2.4 (2.3-2.5)	<0.0001
Binge drinking in the past 30 days vs. no binge drinking in past 30 days (ref)	2.8 (2.6-3.0)	2.6 (2.4-2.7)	0.0056
Did not disclose HIV status to all sex partners in past 12 months vs. Disclosed to all (ref)	3.2 (3.0-3.3)	2.4 (2.2-2.5)	<0.0001
Not 100% adherent to HIV medicines vs. 100% adherent (ref)	2.9 (2.8-3.1)	2.5 (2.4-2.6)	<0.0001
Any injection/non-injection drug use in past 12 months vs. none (ref)	2.6 (2.5-2.8)	2.6 (2.5-2.7)	0.40
Had sex without a condom in the past 12 months vs. Did not have sex without a condom in the past 12 months (ref)	2.5 (2.4-2.6)	2.6 (2.5-2.7)	0.18
Most recent HIV viral load undetectable or ≤200 copies/mL vs. HIV viral load detectable, >200 copies/mL or missing/unknown (ref)	2.6 (2.5-2.7)	2.5 (2.5-2.7)	0.37

Table 1. Bivariate associations between mean internalized stigma and behavioral and clinical outcomes - United States, 2011 (n=4385)

Conclusions: Among HIV-infected adults in care in the U.S., internalized stigma was associated with depression and binge drinking. Moreover, stigma was associated with lack of disclosure of HIV status to sex partners, but was not related to certain factors associated with transmission risk such as viral load and sex without a condom. Targeted interventions to reduce internalized stigma may be beneficial for HIV-infected adults, including older persons, heterosexuals, foreign-born persons, those with health insurance gaps and those recently diagnosed.

1058 Association Between Enacted Stigma and HIV-Related Risk Behavior Among MSM, National HIV Behavioral Surveillance System, 2011

Alexandra B. Balaji; Justin C. Smith; Kristina Bowles; Gabriela Paz-Bailey

US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: Men who have sex with men (MSM) bear a disproportionate burden of the HIV epidemic. Enacted stigma (overt negative actions against sexual minorities) may play an important role in increasing HIV risk among this population. We report data on the association between measures of enacted stigma and HIV-related sexual risk behaviors among MSM in 2011.

Methods: We examined data from 20 cities that participated in the 2011 National HIV Behavioral Surveillance System (NHBS) among MSM. Venue-based, time-space sampling was used to recruit men for interview and HIV testing. We analyzed data from men who reported ≥1 male sex partner in the past 12 months and who did not self-report to be HIV-positive. We used separate GEE models with a robust error variance procedure to estimate prevalence ratios and confidence intervals for the independent associations between three measures of enacted stigma (verbal harassment, discrimination, physical assault) and engagement in each of three sexual risk behaviors in the past 12 months as outcomes: condom-less anal intercourse, ≥4male sex partners, and exchange sex. Models were adjusted for demographic and behavioral characteristics associated with the outcomes.

Results: Of 8922 MSM, 2883 (32.3%) experienced verbal harassment in the past 12 months, 2113 (23.7%) experienced discrimination, and 754 (8.5%) experienced physical assault. MSM who experienced the three measures of enacted stigma were more likely to report the three HIV-related risk behaviors. Condom-less anal intercourse was associated with verbal harassment (adjusted prevalence ratio [aPR] 1.08, 95% confidence interval [CI] 1.03-1.14), discrimination (aPR 1.09, CI 1.05-1.14), and physical assault (aPR 1.09, CI 1.02-1.16). Having ≥4 male sex partners was associated with verbal harassment (aPR 1.14, CI 1.09-1.19), discrimination (aPR 1.14, CI 1.07-1.21), and physical assault (aPR 1.13, CI 103-1.24). Exchange sex was associated with verbal harassment (aPR 1.40, CI 1.21-1.61), discrimination (aPR 1.55, CI 1.28-1.88), and physical assault (aPR, CI 1.46-2.08).

Conclusions: These findings indicate that a sizable proportion of MSM report occurrences of enacted stigma and suggest that these experiences may be associated with HIV-related risk behavior. Taken together, these data indicate a need for interventions that increase the acceptance of sexual minorities in the larger society and facilitate coping with experiences of enacted stigma.

1059 Has Antiretroviral Treatment Scale-Up in Sub-Saharan Africa Reduced HIV-Related Stigma in the General Population? A Cross-Country Analysis

Brian T. Chan[1]; Alexander Tsai[2]; Mark Siedner[2]

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US

Background: HIV-related stigma is associated with reduced uptake of HIV testing, increased risk-taking behavior, decreased adherence to anti-retroviral therapy (ART), and reduced HIV status disclosure. The extent to which ART scale-up in sub-Saharan Africa has resulted in population-level changes in HIV-related stigma remains unclear. To help answer this question, we examined trends in stigma during ART scale-up in sub-Saharan Africa (2003-2013), using population-based data on ART coverage from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and on HIV-related stigma from the Demographic and Health Surveys (DHS) and AIDS Indicator Surveys (AIS).

Methods: We constructed a composite indicator for HIV-related stigma in the general population, defined as the percentage of men and women aged 15-49 in the DHS and AIS who responded positively to at least one of four standardized questions related to stigmatizing attitudes and fears about disclosure. We limited our analysis to countries with at least two datasets in which this composite stigma variable was included. We fitted two linear regression models with country fixed effects, with percentage of men or women reporting HIV-related stigma as the dependent variable, and the percentage of people living with HIV on ART as the explanatory variable.

Results: We analyzed data from 18 sub-Saharan African countries. The median percentage of the general population reporting HIV-related stigma was 89% (IQR, 75-92%) for women and 81% for men (IQR, 66-86%). For each 1% increase in ART coverage, we observed a statistically significant decline in the percentage of women (b=-0.238; 95% CI, -0.394 to -0.082) and men (b=-0.288; 95% CI, -0.488 to -0.089) in the general population reporting HIV-related stigma. This corresponds to a decrease in population reported HIV-related stigma of approximately 2% for each 10% increase in ART coverage.

Conclusions: We observed a significant association between increasing ART coverage and declining HIV-related stigma in the general population. Our findings suggest that an important benefit of ART scale-up may be the diminution of HIV-related stigma in the general population. However, given that stigma remained high in all of the countries under study despite ART expansion, further study of interventions that effectively target HIV-related stigma is warranted.

THURSDAY, FEBRUARY 26, 2015

Session P-W8 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Serosorting and Seroadaptive Behavior: What's Your Position?

1060 Trends in Sexual Behaviors Among Men Who Have Sex With Men in the United States, the Role of Antiretroviral Therapy and Seroadaptive Strategies

Gabriela Paz-Bailey[1]; Maria Mendoza[1]; Binh Le[1]; Charles E. Rose[1]; Teresa Finlayson[1]; Cyprian Wejnert[1]; Henry F. Raymond[2]; Joseph Prejean[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]San Francisco Department of Public Health, San Francisco, CA, US

Background: CDC data from the National HIV Behavioral Surveillance System (NHBS) suggest that condom use has decreased among men who have sex with men (MSM). The reasons for this decrease are not known but may reflect the adoption of risk-reduction strategies other than consistent condom use, such as engaging in unprotected sex only with partners perceived to have the same HIV status as one's own (sero-adaptive behaviors). We used data among MSM participating in NHBS to evaluate changes from 2005 to 2011 in condomless anal sex at last sex.

Methods: MSM were recruited through venue-based sampling in 2005, 2008 and 2011 in up to 21 U.S. cities. Among men reporting ≥1 male partner and self-reporting as HIV-positive or HIV-negative, we evaluated changes in condomless anal sex at last sex with a partner reported to have 1) HIV concordant status (proxy for sero-adaptive behavior), or 2) HIV-discordant or unknown status, by participant's reported HIV status and antiretroviral therapy (ART) use (HIV-positive only). We used GEE modeling with a robust variance estimation, and assumed a Poisson distribution to explore whether temporal changes in the outcomes varied by selected characteristics.

Results: In adjusted analyses among 23,125 HIV-negative MSM, concordant condomless sex at last anal sex increased significantly (20%, 22% and 24%, in 2005, 2008 and 2011, respectively, p<0.001) as well as discordant/unknown condomless sex (7%, 10%, 11%, respectively, p<0.001). Among 3,785 HIV-positive MSM, there were no significant changes in concordant (19%, 21% and 26%, p=0.14) or discordant/unknown condomless sex (14%, 16%, and 14%, p=0.11). Concordant condomless sex increased among MSM on ART (18%, 22%, and 26%, p<0.001) but not among MSM not on ART (21%, 20% and 27%, p=0.11). There were no significant changes in discordant/unknown condomless sex by ART use.

Conclusions: There were modest increases in condomless sex at last sex both with partners of concordant and discordant/unknown HIV status among HIV-negative MSM, and only with a partner of concordant status among HIV-positive MSM on ART. These data suggest that the increases in condomless sex among MSM are in part due to the adoption of sero-adaptive behaviors but that discordant condomless sex is also increasing among HIV-negative MSM. HIV-negative MSM who engage in condomless sex would benefit from having access to risk-reduction interventions, including pre-exposure prophylaxis.

1061 Changes in Condomless Sex and Serosorting Among MSM After HIV Diagnosis

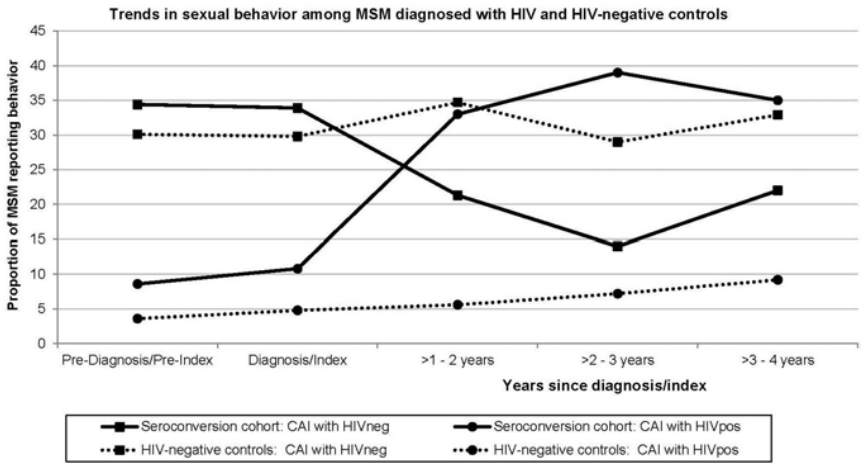
Christine M. Khosropour[2]; Julia C. Dombrowski[2]; David A. Katz[2]; Matthew R. Golden[2]

[1]University of Washington, Seattle, WA, US; [2]University of Washington, Seattle, WA, US

Background: Among men who have sex with men (MSM) diagnosed with HIV, high-risk sexual behaviors may decline in the year after diagnosis, but changes in serosorting post-diagnosis are not well defined. Few studies have assessed changes in these behaviors both pre-diagnosis and for several years after.

Methods: We created a retrospective cohort (seroconversion cohort) of MSM attending an STD clinic in Seattle, WA who tested HIV positive between 2002-2013 and had a negative HIV test ≤2 years prior to diagnosis (pre-diagnosis visit). Potential controls were MSM who never tested HIV-positive and had a negative test ≤2 years prior to a randomly selected index visit. We randomly selected 1,000 controls frequency-matched to the seroconversion cohort based on HIV diagnosis year/index date. Sexual behavior data in the 12 months prior to each visit were collected by clinicians using standardized forms or a computer self-interview as part of routine clinical care. We examined condomless anal intercourse (CAI) with HIV-negative and -positive partners at 5 time points: before diagnosis/index, at diagnosis/index, and each year up to 3 visits after diagnosis/index. We used McNemar's chi-square to compare behaviors reported at the 2 visits before/at diagnosis vs. the 3 visits after diagnosis and used linear regression to examine trends over time.

Results: There were 655 (2.5%) new HIV diagnoses at 26,144 clinic visits where MSM tested for HIV; 186 (28%) men with a new diagnosis tested negative ≤2 years before diagnosis and were included in the seroconversion cohort. The 1,000 persistently HIV-negative controls were selected from 3,083 eligible MSM. In the seroconversion cohort, the percent reporting CAI with HIV-negative partners declined after diagnosis (34% vs 19%, P=.003) while the percent reporting CAI with HIV-positive partners increased (10% vs 35%, P<.001; Figure). Thus, the proportion who serosorted (i.e. reported only HIV concordant CAI) did not change before or after diagnosis (34% vs 35%, P=.85) and remained stable in the years after diagnosis (P-value for trend post-diagnosis=.79). Among HIV-negative controls, serosorting and CAI with HIV-positive partners remained relatively constant.



Conclusions: Among MSM in our clinic, those diagnosed with HIV modified their sexual behaviors post-diagnosis based on partner HIV status and this change was sustained several years after diagnosis. These findings suggest that, among MSM, changes in sexual behavior following HIV diagnosis are large and durable.

1062 Serosorting and Sexual Risk Behavior Influenced by Perceived HIV Serostatus Among MSM

Kathleen A. Brady; Jennifer Shinefeld; Catherine Mezzacappa
Philadelphia Department of Public Health, Philadelphia, PA, US

Background: According to the CDC, unknown HIV serostatus and unprotected anal sex among men who have sex with men (MSM) contribute to high levels of new infections in this population. This study used data from the National HIV Behavioral Surveillance System (NHBS) to analyze the relationship between perceived HIV serostatus and high-risk sexual behaviors among MSM.

Methods: NHBS is conducted annually in 20 metropolitan areas using a standardized survey and free HIV testing to analyze trends in HIV risk behaviors and prevalence among high risk groups including MSM. HIV testing included a rapid test at time of interview and a confirmatory test. We combined data from the 2008 and 2011 MSM cycles in Philadelphia and performed bivariate analyses of sexual risk behaviors at last sexual encounter across perceived HIV serostatus. Perceived HIV serostatus was defined as 'known negative' for a man who had a negative HIV test in the past year, 'known positive' for a man who had ever tested positive for HIV, and 'unknown' for a man who had not had an HIV test in the past year nor previously tested positive. Serosorting is the practice of choosing a partner known to be of the same HIV serostatus in order to reduce the risk of acquiring or transmitting HIV.

Results: Of 1194 respondents, 31.3% were known negative, 5.5% known positive, and 63.2% unknown perceived serostatus. Testing revealed that 3.0% of known negative and 4.4% of unknown perceived serostatus were HIV positive. There were no differences in frequency of insertive anal sex at last encounter across perceived serostatus. Known negative men were less likely to use a condom during receptive anal intercourse (p=0.006). Approximately two-thirds of all respondents knew the HIV status of their most recent partner. Among those who knew their partner's HIV status, serosorting was extremely prevalent: 73.9% of known positive men had sex with an HIV positive partner, compared to 5.6% of unknown, and 4.4% of known negative men, (p<0.0001).

Table 1. Behaviors at last sexual encounter by perceived HIV status

	Known Negative N=373	Known Positive N=66	Unknown N=755	p-value
Actual HIV status				
Negative	97.0% (356/367)	0	95.6% (673/704)	
Positive	3.0% (11/367)	100% (66)	4.4% (31/704)	
Type of partner				
Main	34.3% (71/207)	36.1% (13/36)	37.0% (114/308)	0.37
Casual	52.2% (108/207)	41.7% (15/36)	52.0% (160/308)	
Exchange	13.5% (28/207)	22.2% (8/36)	11.0% (34/308)	
Had insertive anal sex (IAS)	61.0% (219/359)	61.5% (40/65)	59.9% (408/681)	0.92
Did not use a condom during IAS	30.1% (66/219)	37.5% (15/40)	25.5% (104/408)	0.17
Had receptive anal sex (RAS)	52.8% (189/358)	56.9% (37/65)	60.4% (411/681)	0.06
Did not use a condom during RAS	42.1% (80/190)	29.7% (11/37)	29.0% (119/411)	0.006
Relative age of partner				
Younger	31.2% (110/353)	41.5% (27/65)	34.0% (226/665)	0.30
Older	35.7% (126/353)	27.7% (18/65)	30.5% (203/665)	
Same age	33.1% (117/353)	30.8% (20/65)	35.5% (236/665)	
Knew HIV status of partner	64.1% (230/359)	70.8% (46/65)	65.5% (446/681)	0.57
Partner was HIV positive (among those who knew HIV status of partner)	4.4% (10/229)	73.9% (34/46)	5.6% (25/443)	<0.0001

Conclusions: Knowledge of HIV serostatus influences sexual behaviors among MSM, particularly through serosorting. However, over 60% of men surveyed had not been tested for HIV in the previous year and a third of men did not know the HIV status of their most recent partner. Prevention efforts should be tailored to reach those MSM who remain unaware of their HIV status.

1063 Use of the Seroadaptive Strategies of Sexual Positioning and Serosorting by MSM in Nigeria

Cristina M. Rodriguez-Hart[1]; Hongjie Liu[2]; Ifeanyi K. Orazulike[3]; Sam Zorowitz[4]; Sylvia Adebajo[5]; Lindsay Hughes[6]; Stefan Baral[7]; Merlin L. Robb[6]; William Blattner[1]; Manhattan Charurat[1]
[1]University of Maryland School of Medicine, Baltimore, MD, US; [2]University of Maryland School of Public Health, College Park, MD, US; [3]International Center on Advocacy and Rights to Health, Abuja, Nigeria; [4]Massachusetts General Hospital and Harvard Medical School, Boston, MA, US; [5]Population Council, Abuja, Nigeria; [6]US Military HIV Research Program, Bethesda, MD, US; [7]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

Background: Sexual positioning and serosorting are two seroadaptive strategies adopted by some men who have sex with men (MSM) as HIV harm reduction strategies. The current analysis investigated these factors among MSM in Nigeria, where rates of infection are 10 fold higher than in the general population, who participated in the TRUST study.

Methods: Using respondent-driven sampling, 392 eligible MSM were interviewed. A subject was considered to be engaged in sexual positioning if an HIV positive MSM who knew his status prior to the study reported only receptive anal sex for the previous 12 months or an HIV negative MSM who knew his status prior to the study reported only insertive anal sex for the previous 12 months. A subject was considered to be engaged in serosorting if he knew his HIV status prior to the study and reported having only sex partners of the same HIV status. Logistic regression with generalized estimating equations was used to analyze factors associated with engagement in positioning or serosorting.

Results: Of the 390 participants with HIV testing history and who were tested for HIV at baseline, 21% (85/390) were HIV positive and reported knowing their status, 29% (114/390) were HIV negative and reported knowing their status, 23% (89/390) were HIV positive and reported not knowing their status, and 25% (97/390) were HIV negative and reported not knowing their status.

Among HIV positive MSM who knew their HIV status, 21% (18/85) practiced receptive sex only. Among HIV negative MSM who knew their status, 39% (44/114) practiced insertive sex only. Engagement in sexual positioning was associated with older age (OR=2.15; 95%CI: 1.07-4.32), not being married to a woman (OR=2.94; 95%CI: 1.03-8.33), and communication with partners about HIV status (OR=1.84; 95%CI: 1.01-3.36). The 384 MSM who reported any sex partner data generated 1565 sex partner dyads. Serosorting took place only among 192 dyads (12%). Engagement in serosorting was associated with communication with partners about HIV status (OR=3.78; 95%CI: 2.12-6.75) and stronger friendship (OR=1.40; 95%CI: 1.11-1.76).

Table 1. Sexual positioning and serosorting by HIV testing history and HIV serostatus among men who have sex with men (MSM) in Abuja, Nigeria

	Ego Self-Reported Knowing their HIV Status Prior to the Study		Ego Self-Reported Not Knowing their HIV Status Prior to the Study	
	HIV+ Crude % (n)	HIV- Crude % (n)	HIV+ Crude % (n)	HIV- Crude % (n)
Sexual Positioning (n=number of egos)[a]	n = 85	n = 114	n = 89	n = 97
Ego's Sexual Position				
Only insertive (n=103)	15.3 (13)	38.6 (44)	16.9 (15)	32.0 (31)
Only receptive (n=81)	21.2 (18)	20.2 (23)	20.2 (18)	22.7 (22)
Dual Practice (n=201)	63.5 (54)	41.2 (47)	62.9 (56)	45.4 (44)
Serosorting (n= number of ego-alter dyads)[b]	n = 357	n = 452	n = 353	n = 403
Alter's HIV Status				
Positive (n=58)	12.6 (45)	1.3 (6)	1.1 (4)	.7 (3)
Negative (n=415)	19.0 (68)	32.5 (147)	26.3 (93)	26.6 (107)
Unknown (n=1092)	68.3 (244)	66.2 (299)	72.5 (256)	72.7 (293)

[a] 7 egos were excluded from the analysis of sexual positioning. Of the 7, sexual positioning could not be calculated for 5

Conclusions: With this low level of engagement in harm reduction strategies among Nigerian MSM, interventions that promote communication between sex partners to adopt harm reduction and engage the full spectrum of combination prevention strategies promoted by the TRUST intervention are a focus of ongoing study, including how to influence normative behaviors in sexual networks.

TUESDAY, FEBRUARY 24, 2015

Session P-X1 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Paying for Care

1064 Ryan White HIV/AIDS Program Assistance and HIV Treatment Outcomes in the United States

Heather Bradley[1]; Abigail H. Viall[1]; Pascale M. Wortley[1]; Antigone Dempsey[2]; Heather Hauck[2]; Jacek Skarbinski[1]

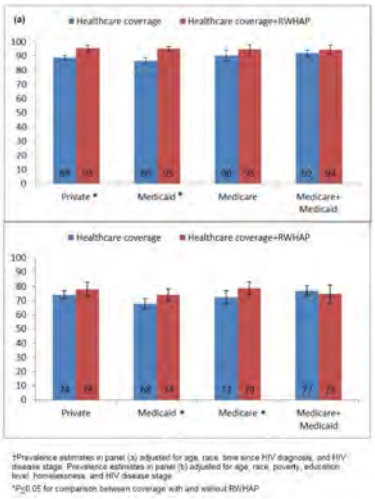
[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]US Health Resources and Services Administration, Rockville, MD, US

Background: The Ryan White HIV/AIDS Program (RWHAP) is the payer of last resort for HIV medical care, medications, and supportive services for uninsured and underinsured persons living with HIV in the United States.

Methods: We assessed the association between RWHAP assistance, alone or in combination with other sources of healthcare coverage, and antiretroviral treatment (ART) prescription and viral suppression (≤ 200 copies/ml). We used 2009–2010 data from the Medical Monitoring Project (MMP), a surveillance system that provides nationally representative data about HIV-infected adults receiving medical care. Data were collected on 8,691 patients through interviews and medical record abstractions. Data were weighted to account for unequal probabilities of selection and both facility and patient nonresponse.

Results: Among adults with HIV infection and recieving medical care in the United States, 40.2% received any RWHAP assistance, and 14.7% relied solely on RWHAP assistance for HIV care (i.e., were otherwise uninsured). Nearly 57% of patients had other health care coverage only, including private insurance (17.0%), Medicaid (16.6%), Medicare (3.3%), or both (9.6%); 3.1% were uninsured with no RWHAP assistance. Overall, 89.6% of patients were prescribed ART, and 72.9% were virally suppressed. Compared to uninsured patients without RWHAP assistance, uninsured patients with RWHAP assistance were significantly more likely to be prescribed ART (43.6% versus 93.7%; $P<0.01$) and to be virally suppressed (36.1% versus 76.9%; $P<0.01$). After adjusting for patient characteristics, those with private insurance, Medicaid, or Medicare were 7%, 9%, and 5% less likely, respectively, to be prescribed ART than those with RWHAP only ($P\leq0.05$). Patients with private insurance, Medicaid, and Medicare were 7%, 15%, and 10% less likely, respectively, to be virally suppressed ($P\leq0.05$) than those with RWHAP only. Patients whose private insurance or Medicaid coverage was supplemented by RWHAP were more likely to be prescribed ART than those without RWHAP supplementation ($P\leq0.05$) (figure 1). Similarly, those whose Medicaid or Medicare coverage was supplemented by RWHAP were more likely to be virally suppressed than those without RWHAP supplementation ($P\leq0.05$).

Figure 1. Adjusted† prevalence of patients (a) on ART treatment and (b) virally suppressed (≤ 200 copies/mL) by health care coverage and Ryan White HIV/AIDS Program (RWHAP) assistance status: Medical Monitoring Project, 2009—2010



†Prevalence estimates in panel (a) adjusted for age, race, time since HIV diagnosis, and HIV disease stage. Prevalence estimates in panel (b) adjusted for age, race, poverty, education level, homelessness, and HIV disease stage.
*P<0.05 for comparison between coverage with and without RWHAP.

Conclusions: Uninsured and underinsured HIV-infected persons receiving RWHAP assistance were more likely to be prescribed ART and virally suppressed than those with some other types of healthcare coverage.

1065 Combining Multisite Payor Data With Clinical Data to Quantify Medicaid Payments for HIV Care

Anne Monroe[1]; Cindy Voss[1]; Richard Moore[1]; Kelly Gebo[1]; Allison Agwu[1]; Richard Rutstein[3]; Victoria Sharp[5]; Stephen Boswell[4]; John Fleishman[2]
The HIV Research Network

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Agency for Healthcare Research and Quality, Rockville, MD, US; [3]The Children's Hospital of Philadelphia, Philadelphia, PA, US; [4]Fenway Health, Boston, MA, US; [5]Wyckoff Heights Medical Center, Brooklyn, NY, US

Background: Costs of care for persons living with HIV (PLWH) have been high historically and may increase as the HIV-infected population ages. Cost estimates based on data from one health care site likely underestimate total expenditures; using insurance claims avoids this limitation. We used Medicaid claims data to comprehensively measure payments for care for PLWH.

Methods: Six sites from the HIV Research Network (HIVRN) participated. Medicaid data were obtained from the sites' states (MD, PA, NY, and MA) and 3 surrounding states per site and matched to HIVRN medical record-based data. Individuals less than 18 and those with Medicare and Medicaid were excluded. Adjusted regression analyses were performed to examine the relationship between total payments and HIVRN demographic and clinical variables.

Results: 6,892 unique identifiers from the HIVRN were submitted; 6,160 (89.4%) had a match in the Medicaid data. The data set included 13,492 person-years of Medicaid insurance claims data from 4,909 adults (66% male; 57% Black, 20% Hispanic, and 15% white; 29% IDU, 28% MSM, 37% HET; median age 44 years, range 18-76) with baseline CD4 cell count of ≤ 200, 200-500 and ≥500 cells/mm^3 in 27%, 43%, and 30%. Mean payment PPY increased over time from $42,914 in 2006 to $47,094 in 2010 (9.7% increase, inflation was 8.2%). Mean payment PPY for patients aged < 50 was $41,061 and for patients aged ≥ 50 was $51,868. Mean payment PPY for patients with CD4 count ≤ 200, 201-499, and >500 cells/mm^3 was $60,000, $42,390, and $35,932. Higher payments for older vs. younger patients in the two highest CD4 cell count categories were observed (p=0.007). Drug payments PPY averaged $12,566 in 2006 and $20,005 in 2010. Overall, ART payments comprised 50% of total drug payments in 2006 and 67% of the total in 2010, with ART payments almost doubling, while payments for inpatient and outpatient care declined significantly. In multivariable linear regression, age category (≥ 50 vs. <50 years), CD4 category (both ≥ 500 vs. ≤ 200 and 201-499 vs. ≤200), year (2010 vs. 2006) and risk factor (both IDU and HET vs. MSM) were significantly associated with higher payments (p<0.05 for all).

Mean Payment per Medicaid Beneficiary by Type of Service, CD4 count, and Age (2006-2010)

Figure 1a. Beneficiaries aged < 50 years

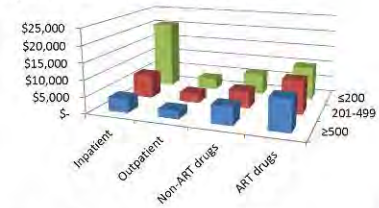
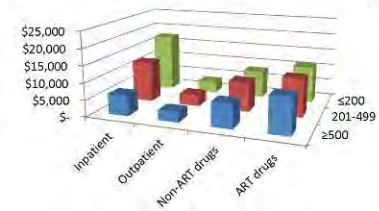
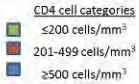


Figure 1b. Beneficiaries aged ≥ 50 years





Conclusions: Payments for care for PLWH remain high, particularly in PLWH with the lowest CD4 counts, emphasizing the importance of effective treatment and immune reconstitution. Payments for older individuals are high and will likely continue to grow as PLWH live longer. Finally, rising ART costs have been offset by lower inpatient and outpatient costs.

1066 Proportionately More Gay Men in Seattle Insured Following the Affordable Care Act

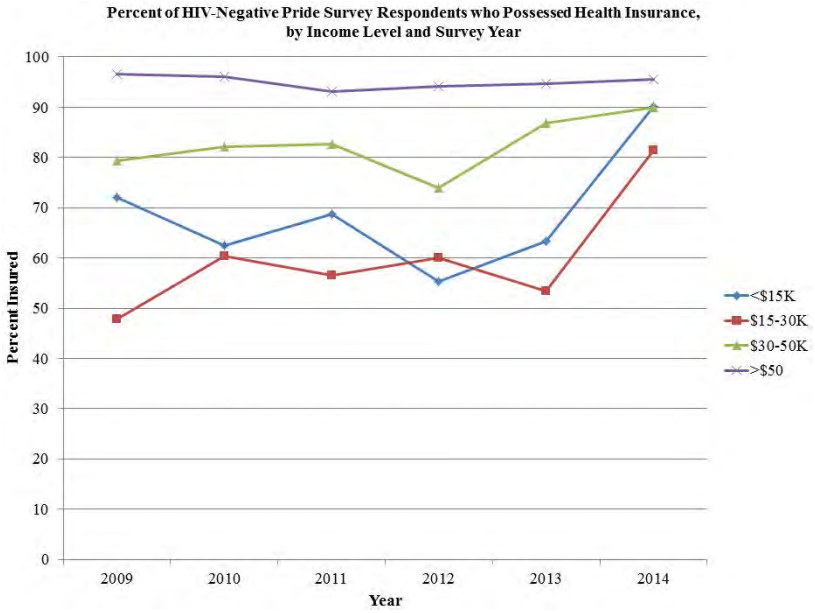
Julia E. Hood[1]; Susan E. Buskin[1]; Elizabeth A. Barash[1]; Julia C. Dombrowski[2]; Matthew R. Golden[2]

[1]Public Health–Seattle & King County, Seattle, WA, US; [2]University of Washington, Seattle, WA, US

Background: The Affordable Care Act (ACA) was established to improve the quality, accessibility, and cost of health care in the United States. Washington ranked among the top 10 states on two ACA implementation metrics: proportion of uninsured selecting an insurance plan through exchange, and percent increase in Medicaid enrollment. We assessed the extent to which ACA impacted men who have sex with men (MSM) in Seattle.

Methods: We analyzed cross-sectional survey data collected annually at the Seattle Pride Parade between 2009 and 2014 (n=2095). Parade spectators who self-identified as a 'man who has sex with men' were eligible to complete a self- or interviewer-administered survey. Respondents were asked if they had health insurance, a regular medical provider, and been impacted by ACA. They were considered 'high risk' if they reported an STD diagnosis, methamphetamine or popper use, 10+ sex partners, or non-concordant condomless anal sex in last year. This analysis excludes self-reported HIV-positive respondents (n=240). We summarize survey responses using descriptive statistics and used multiple logistic and linear regression to identify factors associated having health insurance.

Results: Controlling for age, race, education, income, and HIV risk, respondents in 2014 were significantly more likely to be insured than respondents in prior years (aOR= 3.3, 95% CI= 2.3-4.7, p<0.0001). The income disparity in insurance status narrowed considerably. The percent insured among respondents with an annual income <$30,000 increased from 59% in 2013 to 86% in 2014. Sixteen percent of respondents reported having used the Washington HealthPlanFinder (State ACA) Website, and 12% enrolled in an insurance plan via the website. In 2014, 18% of respondents reported that their health care had improved as a result of ACA; 6% reported that their health care had worsened. After controlling for age and HIV risk level, health insurance status was significantly associated with STD testing in the prior 12 months (aOR=2.1, 95% CI=1.1-4.0, p=0.03) but was unassociated with HIV testing in the prior 2 years (p=0.25). The percent of insured and uninsured respondents *without* a regular medical provider was 17% and 53%, respectively.



Conclusions: The proportion of low-income Seattle MSM with health insurance increased dramatically with institution of the ACA. Despite this, nearly a quarter of MSM reported not having a regular medical provider, highlighting the need to link all MSM to medical care.

1067 Characteristics and Outcomes of Patients Seeking Care at a New "Co-Pay" Convenience Clinic Established to Explore Sustainable Funding Models in Uganda

Rosalind M. Parkes-Ratanshi[1]; Gerald Mukisa[1]; Tom Kakaire[1]; Faridah Mayanja[1]; Adelline Tumikye[1]; Brenda Mitchell[1]; Shadia Nakalema[1]; Walter Schlech[2]

[1]Makerere University College of Health Sciences, Kampala, Uganda; [2]Dalhousie University, Halifax, Canada

Background: 80% of funding for HIV services in Uganda is from international funders but this has plateaued and may now decrease. At the Infectious Diseases Institute we provide free of charge HIV care for 8000 patients, therefore we are exploring models of care to provide HIV services with a focus on long term sustainability. HIV prevalence in Uganda increases with socio-economic status. We explored if HIV patients would be interested in paying for services which are more convenient and if their HIV outcomes could be improved with a more convenient service.

Methods: A routine customer care survey at the IDI clinic revealed that 60% of patients would be willing to pay for more convenient services. We established a physician led co-pay clinic in November 2013 which provided more private HIV services in the evenings for patients at a charge of around US$16 for consultation, with routine drugs and tests for free. In February 2014 we started a junior doctor led out of hours clinic (charge = UD$8). We present the preliminary results of an observational study based on patients attending this clinic.

Results: By end of September 2014, 419 patients had ever attended the co-pay clinics at IDI. 50.6% are female, compared to 63.2% in the general clinic. 22 patients were ART naive and eligible for ART when at time of enrolment (CD4 count <350cells/mm3) and 18 (81%) have started ART. 52 patients are new to IDI services, of these 25 had tested HIV positive in the last 6 months, 25 were receiving ART from other clinics and 2 had been lost to follow up from another clinic. 27 (49%) of the new patients enrolled reported missed appointments or poor adherence to ART prior to joining the clinic. 52 patients had a viral load;13 (25%) were detectable (VL >400 copies/ml). Of these 11 switched to an intensified regimen (with a protease inhibitor+/-raltegravir). Of those switched 5 had an increase in CD4 count, 1 CD4 was stable, 5 have not reached 6 months.

Baseline Characteristics Co-pay Clinic Patients	
Age	41 years (IQR 35,48)
Sex	212 (50.6%)
CD4 count at first private visit	450.5 (IQR 333,649)
ART status	
First line	301 (71.8%)
Second line	61(14.6%)
other	9 (2.1%)
Not on ART	48 (11.5%)

Conclusions: Around 5% of the total clinic population have voluntarily moved from free to co-pay services. Many showed previous poor adherence, no engagement in care or virological failure. There is a higher proportion of men in the co-pay clinic compared to general clinic (P<0.001). 81% patients eligible for ART have started ART. 84.5% of those with a detectable viral load have had their ART regimen intensified. The co-pay clinic is accessing patients who may have problems engaging in care prior previously; there are early indications of improved outcomes in this group.

WEDNESDAY, FEBRUARY 25, 2015

Session P-X2 Poster Session — Poster Hall

2:30 pm – 4:00 pm

Linkage to and Retention in Care

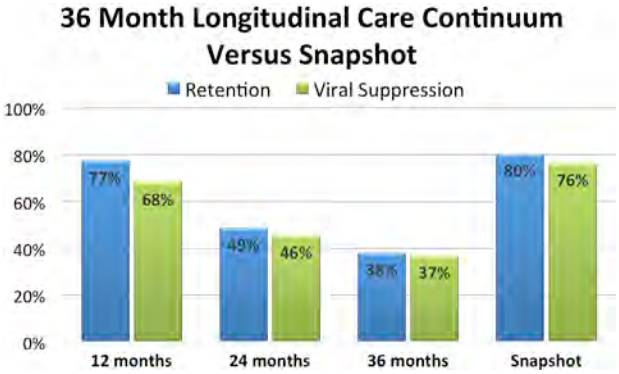
1068 A Longitudinal Approach to Retention and Virologic Suppression Across the HIV Care Continuum

Jonathan Colasanti; Carlos del Rio; Wendy Armstrong
Emory University School of Medicine, Atlanta, GA, US

Background: Currently published HIV care continua are cross-sectional snapshots of the HIV care process in 12 – 15 month time frames. We examined retention and viral suppression in a clinic cohort over 36 months. We hypothesized that rates of retention and suppression would be lower after 36 months than in a single 12-month time period.

Methods: A retrospective cohort study with 36-month follow-up was conducted on patients who enrolled at the Infectious Diseases Center of the Grady Health system (IDP) in the year 2010. Retention for each 12 month period was defined as attending at least 2 provider visits separated by ≥ 90 days. Viral suppression was defined as the last viral load of 12 month period being ≤ 1000 copies/mL. Chi-square tests were performed to evaluate the difference in rates of short-term and long-term retention and viral suppression.

Results: 650 patients were enrolled in 2010 (78.2% male; 82.5% Black; 55% men who have sex with men) with a mean age (SD) of 39 years old (10.6). The percent of patients retained for 12, 24 and 36 months were 77.4%, 48.8% and 38.2% respectively while those achieving viral suppression were 68.3%, 45.5%, and 36.9%. Retention and viral suppression for any single 12 month period were 80.3% and 76.3% respectively. The proportion of patients retained and virally suppressed in a single 12 month time period was statistically significantly greater (p<0.001) than those achieving the same benchmarks at 24 and 36 months.



Graphical representation of retention in care and viral suppression over the course of 36 months compared with retention and viral suppression in any 12-month period (snapshot). The rates of both retention and viral suppression are significantly higher for the 12-month snapshot than for 24 or 36 months.

Conclusions: A great majority of patients in our cohort were able to achieve both retention and viral suppression at a single point in time, however long-term (24 and 36 month) retention and viral suppression were suboptimal. Our data suggest that the current HIV care continuum model may portray falsely optimistic retention and viral suppression rates. The goal of HIV care is maintenance of viral suppression. As a tool for depicting the HIV care process, the care continuum should reflect the benchmarks of retentinon and viral suppression over longer periods of time than 12 - 15 months.

1069 A High Proportion of Persons Diagnosed With Acute HIV Achieve Viral Suppression

Emily Westheimer[1]; Philip J. Peters[2]; Rebekkah Robbins[3]; Sarah L. Braunstein[3]
[1]New York City Department of Health and Mental Hygiene, Queens, NY, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [3]New York City Department of Health and Mental Hygiene, Queens, NY, US

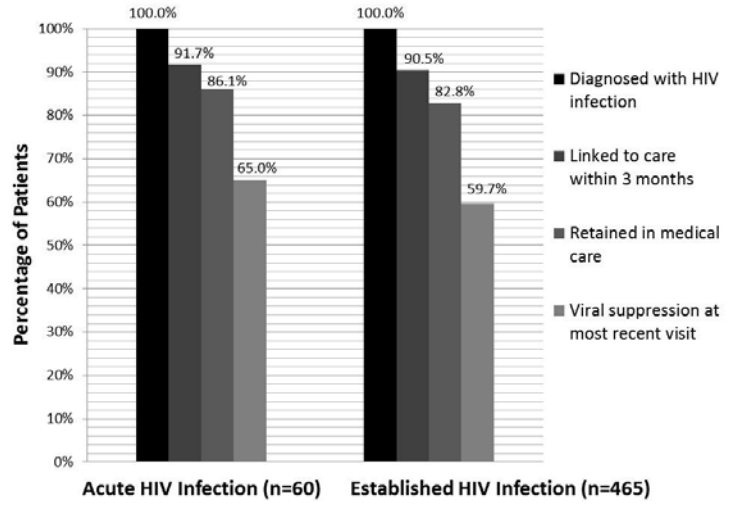
Background: Advances in HIV testing have improved HIV diagnosis in the acute (highly infectious) phase of infection. This analysis sought to determine whether patients with acute HIV infection (AHI) are successfully linked to care and achieve viral suppression rates comparable to patients newly diagnosed with non-acute "established" HIV infection.

Methods: The STOP study was a prospective multi-site study comparing two methods to detect AHI. In New York City (NYC), participants (age ≥ 12 years) at three STD clinics and two community-based testing programs were screened for HIV. Individuals newly diagnosed with either acute (rapid HIV test negative; HIV-1 RNA detectable) or established HIV

infection (rapid HIV test reactive and confirmed) were referred to an HIV care provider. CD4 cell count and viral load laboratory reports received by NYC's HIV surveillance program were used to determine HIV care continuum outcomes. Individuals with a reported CD4 count or viral load were considered linked to care. Retention in care was defined as two CD4 or VL tests ≥ 90 days apart. Viral suppression was defined as a VL < 200 copies/mL. The proportion of patients linked to care, retained in care and achieving viral suppression were compared using chi square and fisher's exact tests.

Results: From October 2011 to October 2013, 525 STOP participants were newly diagnosed with HIV infection including 60 with AHI. A similar proportion of individuals with acute and established HIV infection were linked to care within 3 months of diagnosis (91.7% vs. 90.5%, p=0.78). Among the 36 participants with AHI who had 12 month follow up information, 86.1% (n=31) were retained in medical care and 65% (n=26) were virally suppressed at their most recent visit. Participants with established HIV infection had comparable outcomes (Figure 1). Patients aged 25 or older at diagnosis (vs. <25 years, p<0.01), testing at a facility co-located with treatment services (vs. not co-located, p=0.04) and patients of white race/ethnicity (vs. non-white, p<0.02) were more likely to achieve viral suppression within 12 months. Median time to viral suppression was 175.5 days (AHI) versus 149.5 days (established infection), (p<0.05).

Figure 1. HIV care continuum outcomes among patients diagnosed with acute versus established infection, STOP study, New York City, October 2011-October 2013



Conclusions: We found high rates of linkage to care and viral suppression in this sample and this did not differ for people with acute HIV, compared to those with established HIV infection. Better strategies are needed for youth and racial/ethnic minorities to ensure they receive, and benefit from early HIV treatment.

1070 Drivers of HIV Treatment Success Among a Population-Based Sample of Younger Black MSM

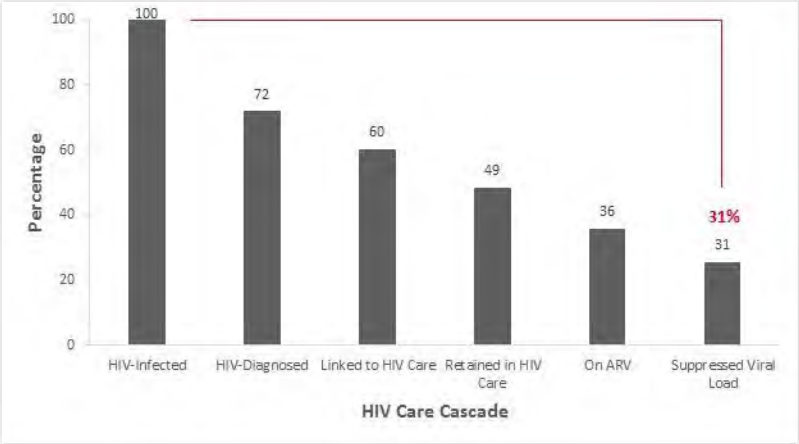
John A. Schneider[1]; Britt Skaathun[1]; Stuart Michaels[2]; Lindsay Young[1]; Keith Green[1]; Ethan Morgan[1]; Robert W. Coombs[3]; Sam Friedman[4]; Edward Laumann[1]
On behalf of UConnect Study Team

[1]University of Chicago, Chicago, IL, US; [2]NORC, Chicago, IL, US; [3]University of Washington, Seattle, WA, US; [4]National Development Research Institute, New York, NY, US

Background: Improving treatment outcomes for younger Black MSM (YBMSM) is critical to controlling the HIV epidemic domestically. A seminal meta-analysis conducted by Millet in 2012 reviewed factors associated with increased rates of HIV among Black MSM and highlighted several disparities compared to white MSM. We examine how these disparate factors are related to HIV treatment continuum metrics from the first population-based sample of YBMSM 16-29 years of age.

Methods: From 2013-2014 a representative sample of YBMSM was generated using Respondent Driven Sampling (RDS) in Chicago (n=626). HIV antibody/Ag and RNA testing were performed using dry blood spots. Outcomes were computed for steps in the treatment continuum including HIV tested, HIV diagnosed, linkage to care within 6 months, retained in care (2 or more visits 3 months apart in 1 year), 30 day adherence to ARVs, and laboratory confirmed viral suppression. RDS-unweighted models examined the associations between key factors known to disparately impact BMSM and each of the continuum metrics independently with observations inclusive of participants unique to each step. These models included age, education, unemployment, homelessness, health care coverage, drug use, incarceration and depression.

Results: YBMSM had a 28% seropositivity rate; 31% of positives were virally suppressed. Treatment continuum outcomes are in Figure 1. Factors associated with HIV diagnosis included older (aOR, 1.12; p=0.001), insured (aOR, 2.31; p=0.001), and drug using (aOR, 1.86; p=0.01) YBMSM. Factors associated with linkage to care included unemployment (aOR, 6.76; p=0.04) and insured status (aOR, 4.24; p=0.04). Those who used drugs were both less likely to be prescribed ARVs (aOR, 0.003; p=0.024) and less likely to adhere to ARVs (aOR, 0.29, p=0.046). There were no factors associated with retention in care or viral suppression.



Treatment Continuum for a population-based sample of younger Black men who have sex with men ages 16-29 in Chicago (n=626).

Conclusions: Treatment continuum metrics among YBMSM are similar to the general HIV infected population. Several structural factors are associated with these metrics such as drug use; some like unemployment may have opposite than anticipated relationships. Notably, metrics such as retention in care and viral suppression are not associated with key structural factors that disproportionately affect YBMSM such as homelessness and incarceration. More research is needed to determine and intervene upon key drivers related to HIV treatment continuum metrics among YBMSM, with particular attention to the diversity of drivers related to each step.

1071 Population-Level HIV RNA and CD4+ Distribution in a Rural Ugandan Community With Widespread Community HIV Testing and Universal ART Access

Vivek Jain[1]; Gabriel Chamie[1]; Gideon Amanyire[2]; Dalsone Kwarisiima[2]; Jane Kabami[2]; Maya L. Petersen[3]; Tamara Clark[1]; Edwin D. Charlebois[1]; Moses R. Kamya[2]; Diane Havlir[1]

[1]University of California San Francisco, San Francisco, CA, US; [2]Makerere University–University of California San Francisco Research Collaboration, Kampala, Uganda; [3]University of California Berkeley School of Public Health, Berkeley, CA, US

Background: The new UNAIDS 90-90-90 initiative (90% diagnosed, 90% on ART, 90% with undetectable viral load [VL]) calls for treatment to achieve 73% overall viral suppression on a population level. We have been conducting community health campaign-based HIV testing and linkage to care, and have enabled access to ART for all persons including high CD4+ T cell counts (>350 cells/uL) (EARLI Study: NCT01479634) starting in 2011 in a rural Ugandan community. We examine trends in viral suppression among community health campaign participants.

Methods: During a 6-day community health campaign in 2014 in Kakyerere Parish, southwestern Uganda, adults (≥18 years) and children were offered HIV testing (Determine, Inverness). In HIV-positive persons, HIV RNA level was measured via a validated fingerprick collection method followed by RT-PCR (Abbott; limit of detection, 1000 copies/mL). Three population viral load metrics were assessed among HIV+ adult residents and non-residents attending the health campaign: (1) proportion of persons with an undetectable VL, VL 1000-10000 c/mL, 10,000-100,000 c/mL, and ≥100,000 c/mL, (2) median VL, and (3) the mean log(VL). CD4+ count was also measured in HIV-positive persons (PIMA, Alere) and compared between community residents and persons from outside the community (where testing campaigns were not conducted and ART was available only for persons with CD4+ counts below government program threshold).

Results: A total of 4897 persons attended the 2014 health campaign (86% coverage among adults based on estimated 2014 census projections). HIV prevalence among adults was 8.5%, and among children was 0.7%. Among community residents with HIV (n=220), 71% had an undetectable VL, increased from 55% in 2012 and 37% in 2011. Overall, 9% had VL 1000-10,000; 11% had VL 10,001-100,000; and 9% had VL>100,000 c/mL. Median VL was undetectable. Mean log(VL) was 3.38 log (95%CI, 3.28-3.49). Among persons living outside the community, only 54% had an undetectable VL (n=13). Median CD4+ count was 511 cells/uL among community adults, and was 417 cells/uL among adults living outside the community.

Conclusions: In a rural Ugandan community with intensive community health campaigns with HIV testing and linkage, and universal ART access, we found viral suppression among HIV+ persons attending health campaigns increased from 37% in 2011 to 71% in 2014. Lower population viral suppression and a lower median CD4+ count were seen in persons living outside the study community.

1072 Facility-Level Factors Influencing Retention in HIV Care in East Africa

Beth Rachlis[1]; Giorgos Bakoyannis[2]; Philippa Easterbrook[3]; R. Scott Braithwaite[4]; Craig R. Cohen[5]; Elizabeth Bukusi[6]; Andrew D. Kambugu[3]; Mwebesa Bosco Bwana[7]; Elvin H. Geng[5]; Paula Braitstein[1]

[1]Academic Model Providing Access to Healthcare program, Eldoret, Kenya; [2]Indiana University, School of Medicine, Indianapolis, IN, US; [3]Infectious Diseases Institute, Kampala, Uganda; [4]New York University, New York City, NY, US; [5]University of California San Francisco (UCSF), San Francisco, CA, US; [6]Kenya Medical Research Institute, Nairobi, Kenya; [7]Mbarara University, Mbarara, Uganda

Background: Retention in HIV care is critical for viral suppression and decreased HIV transmission among people living with HIV. Unfortunately, losses to follow-up (LTFU) remain an important programmatic challenge in many low and middle-income settings. Numerous patient factors have been linked with LTFU, but less is known about associated facility-level factors.

Methods: Using data from the East African International epidemiologic Databases to Evaluate AIDS (IeDEA) Consortium, we sought to identify facility-level factors associated with LTFU from care before and after antiretroviral therapy (ART) initiation. All facilities associated with IeDEA programs in Kenya, Tanzania and Uganda were included. Patients were defined as LTFU if they had no visit within 12 months of the study endpoint for pre-ART patients or 6 months for patients on ART, with no documentation of patient death or transfer. LTFU rates were stratified by country and program. Adjusting for patient-level factors, shared frailty proportional hazard models were used to identify the facility-level factors associated with LTFU for the pre- and post-ART periods.

Results: Data from 88,152 patients and 29 clinics (Kenya 23, Tanzania 3, Uganda 3) were analyzed. Median age at enrollment was 34.9 years (Interquartile Range: 29.0-42.1), 68.3% were women and 61.2% initiated ART. Median LTFU rates for the pre- and post-ART periods were 25.1/100 (95% Confidence Interval (CI): 24.7-26.6) and 16.7/100 (95% CI: 16.3-17.2) person-years respectively. Facility-level factors associated with increased LTFU before and after ART initiation included care provided at the primary level, HIV RNA PCR turnaround time >14 days, and only off-site availability of CD4 testing. Increased LTFU was also observed for the pre-ART period when no nutritional treatment was provided by the facility and TB symptomatic patients were treated within the ART program. After ART initiation, increased LTFU was associated with the facility being open ≤4 mornings per week.

Facility-level factors influencing LTFU in the pre-ART and ART periods

Facility-Level Factor	Pre-ART Period (HR, 95% CI)	ART Period (HR, 95% CI)
Primary vs. secondary level of care	1.23 (1.14-1.33)**	1.30 (1.22-1.39)**
No provision of nutritional treatment vs. provision of nutritional treatment	1.61 (1.15-2.27)*	-
No provision of vitamins vs. provision of vitamins	-	2.27 (1.47-3.45)**
HIV RNA PCR turnaround time >14 days vs. ≤ 14 days	1.14 (1.07-1.20)**	1.30 (1.21-1.41)**
Off-site availability of CD4 count vs. on-site	1.21 (1.11-1.33)**	1.23 (1.09-1.38)*
TB symptomatic patients treated within ART program vs. referred to TB clinic	1.10 (1.01-1.20)*	1.14 (0.98-1.32)
Open ≤ 4 mornings vs. >4 mornings	-	1.37 (1.12-1.64)*

*p<0.05; **p<0.001; Adjusted for male gender, age at enrollment (pre-ART period), age at ART initiation (ART period), WHO stage, year of enrollment and education level. HR=Hazard Ratio, CI=Confidence Interval

Conclusions: Higher LTFU rates were identified in the pre- versus post-ART period. Facility-level factors associated with LTFU both before and after ART initiation included the level of care of the facility and availability and timeliness of labs. Our findings have implications for the development of facility-based strategies to improve retention in pre- and ART care. This can help to improve the proportion of patients initiating ART who achieve viral suppression.

1073 Patient Retention in HIV Care Is Related to Point of Diagnosis in Western Kenya

Becky L. Genberg[1]; Hana Lee[1]; Fatma Some[2]; Joseph Hogan[1]; Paula Braitstein[3]

[1]Brown University, Providence, RI, US; [2]Moi University School of Medicine, Eldoret, Kenya; [3]Indiana University, School of Medicine, Indianapolis, IN, US

Background: Home-based counseling and testing (HBCT) successfully diagnoses HIV earlier than provider-initiated (PITC) and voluntary counseling and testing (VCT). However, it is unknown whether patients entering care from HBCT have better retention compared with patients entering care from other testing modalities. The objective of this study was to determine the impact of point of diagnosis (i.e., HIV testing program) on retention among patients in western Kenya.

Methods: AMPATH (Academic Model Providing Access to Healthcare), a partnership between Moi University, Moi Teaching and Referral Hospital and a consortium of North American institutions, has provided HIV care to over 160,000 individuals in western Kenya since 2001. This retrospective analysis included all individuals ≥13 years enrolled in care between January 2008-September 2013, with data available on point of diagnosis. Lost-to-follow-up (LTFU) was defined as no clinical contact for at least 90 days following a missed scheduled return, without any information on vital status. Survival analysis methods using Cox regression were employed to estimate the impact of point of diagnosis on LTFU and mortality while adjusting for likely confounders. LTFU analysis was limited to those in care ≥ 90 days. Censoring included death and administrative censoring.

Results: The full sample included 19,425 individuals, of whom 64% were female, with median age of 38 years and median CD4 count at baseline of 225 cells/ml^3. The incidence of LTFU was 7.3, 9.3, and 11.2 per 100 person-years for HBCT, VCT, and PITC, respectively, over a median of 2 years in care. Cox regression modeling adjusting for age (<30, 30-45, >45), sex, marital status, disclosure of HIV, electricity/water in the home, number of people in the household, BMI (<25, 25-30, >30), CD4 count and WHO stage at baseline revealed that patients entering care from PITC (adjusted hazard ratio (AHR)=1.24, 95% CI: 1.03,1.50) were more likely to be LTFU compared to HBCT.

Conclusions: Patients who enrolled in care following diagnosis in HBCT and VCT have similar rates of retention, however those entering from PITC were more likely to become LTFU. Additional efforts to track and retain patients entering care from PITC may be warranted.

1074 Successful Down-Referral Even Among Patients With Virologic Failure in South Africa

Jonathan Colasanti[1]; Darius McDaniel[2]; Brent Johnson[2]; Henry Sunpath[4]; Carlos del Rio[1]; Vincent C. Marconi[1]

[1]Emory University School of Medicine, Atlanta, GA, US; [2]Emory University Rollins School of Public Health, Atlanta, GA, US; [3]Emory University Rollins School of Public Health, Atlanta, GA, US; [4]McCord Hospital, Durban, South Africa

Background: In resource-limited settings, provision of HIV care and antiretroviral therapy (ART) is shifting from specialized programs to the local sector. Decentralized care is critical for long-term programmatic sustainability. This extra step can be disruptive for patients who have established care with providers at the referring clinic especially if experiencing treatment complications. Real-world experience of this process is lacking in this vulnerable population. We examined the rate of re-linkage for patients receiving ART after a clinic closure, focusing on those with virologic failure (VF). We hypothesized that fewer patients overall would establish care at the down-referral clinic (re-linkage) than previously reported. Those with history of VF and poor adherence would be at greater risk of failure of down-referral.

Methods: We conducted secondary analyses on a study of predictors of virologic failure in South Africa. We examined individual-level factors' (survey and chart review) relation to re-linkage. In the parent study, after 5 months of first-line ART cases had VL≥1000 copies/mL and controls VL≤1000 copies/mL. The primary outcome was re-linkage, defined as self-reported attendance to the new clinic. We used two-sample tests to assess the statistical independence of select patient-level variables and failure to re-link. Variables that achieved statistical significance in the univariate analysis along with important epidemiologic variables were included in a multivariate logistic regression model.

Results: The study cohort consists of 458 patients, 158 cases and 300 controls. Table 1 shows study population characteristics. 436 (95%) patients re-linked to care. In the univariate analysis patient satisfaction with original clinic, case-control status, duration of ART, and adherence were significant. In the multivariate analyses, not being pleased with clinic (OR 3.24, 95% CI 1.19–8.82), shorter ART duration (OR 1.04, 95% CI 1.00–1.07), and poor adherence (OR 3.85, 95% CI 1.20–12.36) remained significant in their association with failing to re-link to care at the down-referral site.

Domain / Variable	Successfully re-linked to care	Failed to re-link to care (LTFU or Died)	p-value
Total (N)	436	21	
Demographics			
Age at enrollment			
Mean ± SD (N)	39.7 ± 9.1 (436)	37.3 ± 8.8 (21)	0.23
< 35 years old (% yes)	28.9%	38.1%	0.46
Gender (% female)	64.7%	61.9%	0.82
Race (% black)	99.1%	95.2%	0.21
Socioeconomic			
Education			
≥ 9 years (% yes)	83.3%	95.2%	0.22
Income (% yes)	78.9%	71.4%	0.42
Own or rent own home (% yes)	50.5%	42.9%	0.51
Transport to clinic			
Own car or walk (% yes)	15.4%	4.8%	0.34
Own car or friend's car (% yes)	13.8%	4.8%	0.34
Payor for ARVs			
Patient alone (% yes)	78.7%	76.2%	0.79
Patient or family (% yes)	97.5%	100.0%	1.00
Psychosocial			
Pleased with clinic (% yes)	81.7%	52.4%	0.0029
Active in faith (% yes)	59.2%	47.1%	0.33
Ever used traditional meds (% yes)	58.3%	47.6%	0.37
Marital status			
Married (% yes)	20.2%	19.0%	1.0
Married or lives with partner (% yes)	34.2%	42.9%	0.48
Alcohol use (% social use*)	4.1%	9.5%	0.23
HIV education (% w/ much or some)	98.6%	100%	0.49
Depression (% w/any level depression)	38.3%	47.6%	0.49
Biomedical			
Tuberculosis (% yes)	45.0%	57.1%	0.37
Any AIDS condition (% yes)	65.1%	81.0%	0.16
CD4 at enrollment (% < 200 cell/μL)	28.0%	38.1%	0.33
Prior virologic failure (% yes)	67.2%	33.3%	0.0035
Medications			
Access MPR (median [IQR])	1.0 [1.0 – 1.1]	1.0 [1.0 – 1.0]	0.086
Adherence pill count ratio (median [IQR])	1.1 [1.1 – 1.2]	1.0 [1.0 – 1.1]	0.0053
ART duration (mean ± SD)	30.7 ± 24.5	17.5 ± 15.5	0.0041

Table 1. Characteristics of the population.

*Social use considered using alcohol on weekends or less frequently; LTFU, lost to follow up; SD, standard deviation; ARV, antiretrovirals; MPR, medication position ratio

Conclusions: Overall, linkage to the down-referral site was high. Patient dissatisfaction with clinic and poor adherence were independently predictive of failure to re-link to care upon down-referral but VF was not. In a country with over 2 million on ART, even a small percentage failing down-referral may be problematic and it will be important to identify those at high risk of loss to follow up.

1075 Retention in a Decentralized HIV Care and Treatment Program in North Central Nigeria

Patricia Agaba[1]; Becky L. Genberg[2]; Solomon Sagay[1]; Oche Agbaji[1]; Nancin Dadem[3]; Grace Kolawole[3]; Prosper Okonkwo[3]; Seema Meloni[4]; Phyllis Kanki[4]; Norma C. Ware[5]

[1]University of Jos, Jos, Nigeria; [2]Brown University, Providence, RI, US; [3]AIDS Prevention Initiative, Abuja, Nigeria; [4]Harvard School of Public Health, Boston, MA, US; [5]Harvard Medical School, Boston, MA, US

Background: Rapid expansion of antiretroviral therapy (ART) in Africa has improved outcomes for HIV/AIDS, with decentralization as a key strategy for improving treatment access. Decentralization refers to expansion of ART delivery from tertiary to secondary and primary health care (satellite sites). We describe the retention of adult patients in a "hub-and-spoke" decentralization model in north central Nigeria.

Methods: Data from clinical records between 2008-2012 were used to examine retention using two measures. Retention was defined as: 1) gaps between visits of <180 days, and 2) visit constancy (cumulative proportion of 6-month intervals with at least one clinical visit). Standard descriptive statistics were used to describe the sample and examine differences between tertiary and decentralized sites. Logistic regression analysis with generalized estimating equations was used to estimate the effect of decentralization on gaps and visit constancy (≥80% vs. <80% periods with ≥1 visit), while controlling for patient age, sex, WHO stage and previous ART at baseline.

Results: There were 18,158 patients with 54% enrolled at the tertiary site. The median age of the cohort was 37 years and 66% were female. Thirty-five percent were in WHO stages 3 or 4 and 9% had previous ART experience at baseline. The median time in care was 567 days. Overall, 7.1% of visits were ≥180 days apart, with the tertiary site having a higher proportion of gaps compared to satellite sites (9.5% vs 4.3%, p<0.0001), while the satellites had a higher frequency of periods with at least one visit compared to the tertiary site (95.1% vs 93.2%, p<0.0001). In adjusted analysis enrollment at the tertiary site (OR = 3.73, 95% CI: 3.46-4.02), and previous ART experience (OR=1.17, 95% CI: 1.06-1.29) were associated with gaps in care. Patients at the tertiary site were also 2 times more likely to have <80% of periods without a clinical visit (OR=2.05, 95% CI: 1.78-2.37).

Conclusions: With the hub-and-spoke model of decentralization, retention at satellite sites was better than at the tertiary care site. Patients in decentralized sites had fewer gaps between visits and were more likely to maintain constancy of care over time. Further research is needed to understand the barriers to optimal retention at the tertiary site in order to achieve care objectives.

1076 Patient Level Findings: Pre-ART Mortality and Its Determinants in Tanzania Public-Driven HIV Care Program (2004-2011)

Bonita K. Kilama[1]; Candida Moshiro[2]; Jim Todd[4]; Angela Ramadhani[1]; Donan Mmbando[3]

[1]National AIDS Control Program, Dar es Salaam, United Republic of Tanzania; [2]Muhimbili University of Health and Allied Sciences, Dar es Salaam, United Republic of Tanzania; [3]Ministry of Health Of Social Welfare, Dar es Salaam, United Republic of Tanzania; [4]London School of Hygiene and Tropical Medicine, London, United Kingdom

Background: Limited information is available on patients prior to the start of anti-retroviral therapy (ART), as monitoring of HIV care services has mainly focused on ART initiation and subsequent patient survival. Tanzania has unique data from the national care and treatment clinic (CTC) program for pre-ART HIV positive clients. This analysis reports mortality and determinants of mortality among HIV infected adults prior to ART initiation.

Methods: A retrospective cohort of HIV infected adults (aged 15 years or more) enrolled in Tanzanian CTC prior to ART initiation from November 2004 to December 2011. Patient characteristics at the time of enrolment were described and time from CTC enrolment to death prior to ART initiation used to estimate mortality rates and 95% confidence intervals (95% CI) from Cox proportional hazards regression models. Adjusted Hazard Ratios (AHR) were obtained after adjustment for age, sex, WHO stage CD4 counts, BMI, TB screening and functional status at enrolment.

Results: From 348 health facilities, a total of 526,059 HIV positive adults (67% females) were enrolled in CTC prior to receiving ART. The majority (85%) had working functional status, 82% had a CD4 count within three months of enrolment and 93% were screened for TB at every visit. The overall mortality rate was 37.6 deaths per 1000 person years (95% CI 36.9 - 38.3). Through the years mortality has ranged from 32.0 to 60.4 deaths per 1000 person years. Independent predictors of pre-ART mortality were: WHO stage 3 (AHR=2.37; 95% CI 1.94-2.90), WHO Stage 4 (AHR=4.53; 95% CI 3.64-5.64), female sex (AHR=0.62; 95% CI 0.56 -0.70), CD4 count ≥200 (AHR=0.17; 95% CI 0.15-0.20) and weighing more than 45kg at CTC enrolment (AHR=0.53; 95% CI 0.46-0.62) were significantly associated with a lower hazard of death

Conclusions: Mortality among patients in the pre-ART phase was high, especially among those with low CD4 counts, and at WHO stage 3 and 4. This indicates the need to initiate ART before patients get very sick. Analyzing routinely collected electronic information in Tanzania for pre-ART mortality and its predictors provides information for policy makers to drive program improvements and to establish effective interventions for patients in the pre ART phase.

1077 Impact of the Ebola Outbreak on the Quality of Care of People Living With HIV Taking Antiretroviral Treatment at Donka National Hospital in Conakry, Guinea

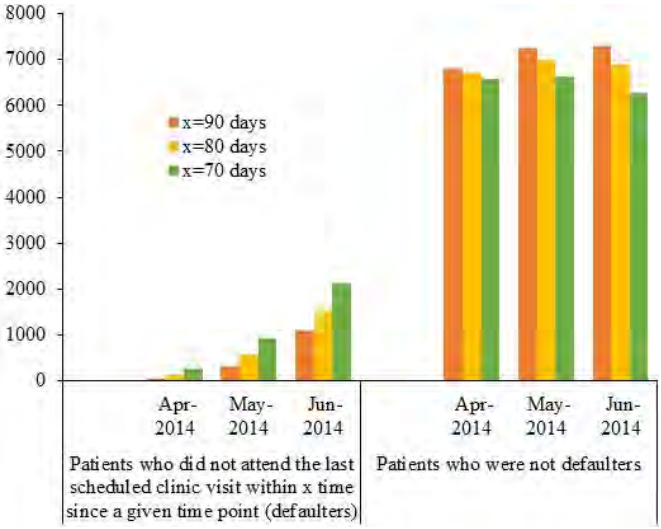
Mohamed Cisse[2]; Mohamadou Saliou Diallo[4]; Cheick Tidiane Tidiane[3]; Cece Kpamou[4]; Justeau Dimitri[4]; Eric Dortenzio[1]; **Jacques D. Ndawinz**[1]

[1]Solthis International NGO, Paris, France; [2]Hôpital National de Donka, Conakry, Guinea; [3]Ministre de la Santé et de l'Hygiène Publique, Conakry, Guinea; [4]Solthis NGO, Conakry, Guinea

Background: Routine monitoring of people living with HIV (PLHIV) taking antiretroviral therapy (ART) is essential to improve the quality of care in the context of Ebola outbreak in Guinea. The Guinea Ministry of Health with Solthis International NGO conduct supervisory visits to all public HIV facilities to strengthen access to care and quality of reported data. Donka national hospital (DNH) is the largest HIV facility in Guinea and is the only isolation and treatment center for Ebola patients in Conakry. From April to June 2014, 55 Ebola confirmed cases were admitted at DNH. The objective of this study was to assess the impact of the Ebola outbreak on the quality of care of PLHIV taking ART in Conakry.

Methods: Prescriptions of ART-patients attending the pharmacy unit of DNH during January to June 2014 were reviewed to gather visit schedules, antiretroviral regimen, and individual information. A defaulters was defined as a patient who did not attend the last scheduled clinic visit within *x* time since a given time point. We considered three lengths of time: x=70, 80, or 90 days. We described PLHIV's follow-up at DNH during the first months of Ebola outbreak.

Results: From January to June 2014, 15384 prescriptions of 8403 ART-patients were reviewed. Sixty three percent were female and the median age was 37 years [interquartile range (IQR):30-46]. The common ART regimens were AZT+3TC+NVP (53%) and TDF+3TC+EFV (28%). Median duration between two consecutive visits was 61 days (IQR: 57-65). The number of visits in clinic/pharmacy decreased from 3062 in April to 2794 in June. When the length of time x=90 days, the proportion of defaulters increased from 1% in April to 15% in June, from 2 to 22% when x=80 days and from 4 to 34% when x=70 days.



The number of patients who did not attend the last scheduled clinic visit within *x* time since a given time point (defaulters) at Donka national hospital, period April-June 2014

Conclusions: From January to June, it seems there is a trend of an increase in the number of defaulters which could be attributed to the Ebola outbreak. Data and analysis for July, August and September will be updated to confirm this result. We recommend that timing visits, number of visits in clinic/pharmacy and defaulters should be continuously measured in order to identify eventual changes, during this Ebola outbreak. New strategies, such as 3 months ART deliveries and mobile clinics should be considered in Guinea to ensure the continuum of care of PLHIV.

1078 The African Diaspora Health Initiative: Enhancing Access to Health Care for African and Caribbean Immigrant Populations in Philadelphia

Helena Kwakwa; Rahab Wahome; Oumar H. Gaye; Natasha Z. Mvula

Philadelphia Department of Public Health, Philadelphia, PA, US

Background: Travel and immigration to the US from areas of the world with higher prevalence of HIV is growing. Many persons in the US from resource-poor countries have limited access to health care including HIV testing. We describe the African Diaspora Health Initiative (ADHI), a project of health screening, integrated HIV testing and linkage to care in the African and Caribbean communities of Philadelphia.

Methods: Launched in 2011, ADHI is a series of Clinics Without Walls (CWW) conducted in settings where African and Caribbean persons are scheduled to gather. Individuals are screened for hypertension, diabetes and HIV. A Project Clinician meets with individual participants to advise them on lifestyle changes including risk reduction. All those returning an abnormal test result or found to have any other health needs are referred to the public city health centers of Philadelphia, and are subsequently followed up to ensure attendance. We present project outcomes data for the first three project years.

Results: Between March 2011 and September 2014, 4,100 first generation African and Caribbean persons were screened in 299 Clinics Without Walls. Of these, 520 were referred for further care and 467 attended an initial medical visit. Acceptance rate for HIV testing was 92%. Previously undiagnosed HIV was detected in 95 participants, and 93 of these were successfully linked to care. Rates of hypertension ranged from 21.6% among African men to 26.4% for Caribbean women. Diabetes rates ranged from 6.7% in African women to 14.6% in Caribbean men. HIV prevalence was lowest among Caribbean women at 0.5% and highest for Caribbean men at 8.6%. Among the 467 linked to care, chronic Hepatitis B prevalence was 13% among Africans and 2% among Caribbean individuals.

Conclusions: Access to care for immigrants as they integrate into US society is critical, and HIV testing must be included in this care. With the lifting of the HIV entry ban in 2010, novel strategies to provide testing are important, and integrating HIV testing into a larger access to health care initiative is not only needed but is accepted by the target population. Our current "test and treat" approach works for this marginalized population only to the extent that they access any care at all. Utilizing Clinics Without Walls facilitates the process since it eliminates the need to convene the target population. This model may be modified in resource-rich countries to engage immigrants from resource-poor countries in HIV testing and in care.

THURSDAY, FEBRUARY 26, 2015

Session P-X3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Guidelines and Their Implementation

1079 Starting ART at 500 CD4 in Southern Africa: What Is the Impact on ART Eligibility?

Helena Huerga[1]; David Maman[1]; Gilles Van Cutsem[2]; Beatrice Kirubi[3]; Charles Masiku[4]; Ruggero G. Giuliani[2]; Irene Mukui[5]; Benson Chilima[6]; Elisabeth Szumilin[7]; Jean-François Etard[1]

[1]Epicentre, Paris, France; [2]Médecins Sans Frontières, Cape Town, South Africa; [3]Médecins Sans Frontières, Nairobi, Kenya; [4]Médecins Sans Frontières, Lilongwe, Malawi; [5]National AIDS and STDs Control Program, Nairobi, Kenya; [6]Ministry of Health, Lilongwe, Malawi; [7]Médecins Sans Frontières, Paris, France

Background: 2013 WHO guidelines recommending antiretroviral therapy (ART) initiation at 500 CD4/μl and PMTCT option B+ are not yet applied in many countries. Direct evaluation in population of the impact on ART eligibility is critical to inform program's decisions and validate model predictions. We present estimates of ART eligibility according to current and new ART guidelines from 3 population based studies.

Methods: Cross-sectional surveys in Ndhiwa (Kenya), KwaZulu-Natal (South Africa) and Chiradzulu (Malawi). Persons aged 15-59 years were eligible. Face-to-face interviews were followed by rapid HIV testing on site and further tests on laboratory. ART intake was self-reported in Kenya and Malawi and blood-tested in South Africa. ART eligibility was defined as individuals eligible for ART among HIV positive. ART was initiated at 350 cells/μl in the 3 countries at the time of the surveys; PMTCT options were A in Kenya, B in South Africa and B+ in Malawi. ART coverage was defined as individuals on ART among eligible.

Results: In total 19,057 individuals were included: 6139 in Kenya, 5649 in South Africa and 7269 in Malawi. HIV prevalence was 24.1% (95%CI 22.9-25.2) in Kenya, 25.2% (95%CI: 23.6-26.9) in South Africa and 17.0% (95%CI: 16.1-17.8) in Malawi. ART coverage was 70.8% in Kenya, 75.0% in South Africa, and 80.4% in Malawi. Higher in women compared to men: 66.7% vs 60.7% (p=0.07) in Kenya, 78.5% vs 63.9% (p<0.001) in South Africa and 83.3% vs 72.2% (p<0.01) in Malawi. Lower in aged<35 years compared to ≥35years: 52.1% vs 74.6% (p<0.001) in Kenya, 64.3% vs 84.3% (p<0.001) in South Africa, 73.6% vs 84.3% (p<0.001) in Malawi. New ART guidelines would lead to an increase of ART eligibility ranging from 7.6% (from 80.4% to 88.0%) in Malawi, 10.7%(from 69.4% to 80.1%) in South Africa to 21.8% in Kenya (from 60.0% to 81.8%). This increase would be higher in people aged <35 years compared to ≥35 years (table). Test and treat strategy would involve a further increase of 12% in Malawi, 20% in South Africa and 18% in Kenya.

	<35 years			≥35 years		
	Current %	WHO 2013 %	Difference %	Current %	WHO 2013 %	Difference %
Kenya	48.9	78.9	30.0	71.8	85.0	13.2
South Africa	61.5	76.7	15.2	78.3	85.7	7.4
Malawi	77.2	82.8	4.6	83.6	91.3	7.7

ART eligibility rates by age group according to current (at the time of the survey) and WHO 2013 guidelines in 3 African countries

Conclusions: Our studies suggest that the implementation of the 2013 WHO guidelines on adults would not represent a major difference in the proportion of ART eligible individuals particularly in some contexts such as the sites of South Africa and Malawi where option B has already been implemented. The application of the new guidelines could be less costly than initially thought using models and it would make a step forward towards the control of the HIV epidemic in the region.

1080 Impact of South Africa's HIV Treatment Guidelines on Early Losses: A Cohort Analysis

Ingrid T. Katz[1]; Richard Kaplan[2]; Garrett Fitzmaurice[4]; Dominick Leone[3]; David R. Bangsberg[1]; Linda-Gail Bekker[2]; Catherine Orrell[2]

[1]Harvard Medical School, Cambridge, MA, US; [2]Desmond Tutu HIV Foundation, Cape Town, South Africa; [3]Boston University School of Medicine, Boston, MA, US; [4]Harvard School of Public Health, Boston, MA, US

Background: South Africa (SA) has the world's largest antiretroviral treatment (ART) program. Prior to 2011, the immunological threshold for ART eligibility in adults was a CD4 count ≤ 200 cells/μl. In September, 2011 the CD4 threshold was increased to ≤ 350 cells/μL, and starting in 2015 it will again be increased to ≤500 cells/uL. While access to ART has expanded, it is unknown if these changes have influenced patients' willingness to engage in care. We hypothesized that increasing the CD4 threshold to access ART would increase early discontinuation of treatment due to greater risk for loss among those with a higher CD4.

Methods: We performed a retrospective cohort analysis of treatment-naive, non-pregnant, individuals who tested positive for HIV and were referred to the Hannan Crusaid Treatment Centre in Cape Town, SA over a five-year period, inclusive of the period when CD4 guidelines were changed. Data were abstracted from electronic records and paper charts, including baseline CD4 at referral, World Health Organization (WHO) stage, decision-making regarding ART initiation, and early discontinuation of treatment (< 16 weeks on ART, confirmed through patient tracking involving up to 3 home visits).

Results: 4025 HIV-infected individuals who underwent CD4 testing between Jan 2, 2009 - Dec 31, 2013 were included. Overall, 90.4% initiated ART, of whom 1.6% died upon initiating ART, and 17.7% had early discontinuation of treatment. Patients in the later sub-cohort were significantly more likely to discontinue care <16 weeks into treatment (19.8% vs. 15.8%, p=.002, see **Table 1**). After controlling for baseline CD4, WHO stage, and age this effect remained significant (Adjusted OR [AOR]= 1.30, 95%CI: 1.09 – 1.55). When the analysis was restricted to include only those individuals in the later cohort who met earlier CD4 threshold (CD4<200 cells/μL), the effect remained (AOR=1.34, 95% CI: 1.06-1.67).

Table 1: Early Losses in Care in Cape Town, South Africa

	Total Cohort (n=4025)	Adults who qualified for ART before CD4 guideline change (n=2123)	Adults who qualified for ART after CD4 guideline change (n=1902)	p-value
Initiated ART	3640/4025 (90.4%)	1924/2123 (90.6%)	1716/1902 (90.2%)	0.70
In care for >16 wks	2938/3640 (80.7%)	1577/1924 (82.0%)	1361/1716 (79.3%)	0.05
Stopped care <16 wks	644/3640 (17.7%)	305/1924 (15.8%)	339/1716 (19.8%)	0.002
Died <=16 weeks	58/3640 (1.6%)	42/1924 (2.2%)	16/1716 (0.9%)	0.004
No ART Initiated	385/4025 (9.6%)	199/2123 (9.4%)	186/1902 (9.8%)	0.70
Died pre-ART	99/385 (25.7%)	68/199 (34.2%)	31/186 (16.7%)	0.0002

Conclusions: Over one-quarter of this cohort never achieved the long-term benefits of ART and viral load suppression due to early mortality, ART discontinuation < 16 weeks, or ART non-initiation. Early discontinuation of ART was significantly higher in the later cohort, although this trend did not appear to be based on CD4 counts at ART initiation. These findings support continued research on understanding socio-behavioral and structural factors driving trends in early losses in care over time in South Africa.

1081 Mortality Across Two ART Trials Enrolling at ≤200 vs ≤350 CD4 cells/uL in Kenya

Rachel A. Silverman[1]; Michael Chung[1]; James N. Kiarie[2]; Nelly Yatich[1]; Julia Njoroge[1]; Catherine Kiptiness[1]; Samah Sakr[3]; Grace John-Stewart[1]; Lisa Frenkel[1]

[1]University of Washington, Seattle, WA, US; [2]University of Nairobi, Nairobi, Kenya; [3]Coptic Hospital, Nairobi, Kenya

Background: In 2011, Kenyan HIV treatment guidelines changed from initiating ART at a CD4 of ≤200 to ≤350 cells/uL. We compared 6-month mortality in 2 research cohorts, one enrolled before and one after the 2011 ART initiation guidelines changed. We hypothesized that following the new guidelines, 6-month post-ART mortality would be lower.

Methods: HIV seropositive adults were enrolled in 2 clinical trials at the Coptic Hope Center, Kenya, in 2006 (drug adherence intervention) and 2013 (drug resistance testing intervention, ongoing). In both trials, participants were enrolled prior to ART initiation and started ART following enrollment. Missed visits were investigated to determine if the participant had died using standardized procedures. Linear regression was used to compare mean baseline CD4 count and Cox proportional hazards regression was used to compare 6-month mortality between the two studies. Subjects who enrolled after January 31 2014 were omitted from the analysis.

Results: There were 362 and 379 participants in 2006 and 2013 cohorts with at least 6 months of follow-up time. 25 participants in 2013 and none from 2006 were missing a baseline CD4 count. The proportion of female participants in each cohort was 66% and 37%, in 2006 and 2013 respectively. The distribution of subjects and deaths by study and CD4 count is shown in Table 1. The mean baseline CD4 count was 73 cells/uL higher (95% CI: 56, 89; p<0.001) in 2013 (199 cells/uL) vs. 2006 (126 cells/uL). The difference in mean CD4 remained approximately the same (72 cells/uL) when controlling for sex and age.

Within 6 months of enrollment, 18 participants died in the 2006 cohort and 20 participants died in the 2013 cohort. The incidence rate of death was 11.7 in 2013 and 10.7 in 2006 per 100 person-years (IRR=1.1, 95% CI: 0.55, 2.2). The hazard ratio (HR) of death comparing 2013 to 2006 was 1.1 (95% CI: 0.57, 2.0; p=0.832). When adjusting for baseline CD4 count, age and sex, the HR was 1.27 (95% CI: 0.57, 2.8, p=0.551). Higher CD4 count was significantly associated with a lower risk of death in all models (p<0.01).

Table 1. Distribution of CD4 count (cells/uL) at enrollment by study cohort

CD4 Count	All Subjects		Deaths	
	2006	2013	2006	2013
Median (IQR)	120 (65, 183)	200 (88, 283)	86 (21, 106)	52 (31, 142)
<50	71 (20%)	54 (15%)	6 (33%)	7 (47%)
50-99	83 (23%)	41 (12%)	5 (28%)	4 (27%)
100-149	69 (19%)	35 (10%)	3 (17%)	1 (7%)
150-199	77 (21%)	49 (14%)	2 (11%)	2 (13%)
≥200	62 (17%)	175 (49%)	2 (11%)	1 (7%)
Total	362 (100%)	354 (100%)	18 (100%)	15 (100%)

**14 subjects from 2006 and 66 subjects from 2013 had <6 months of follow-up. 25 subjects from 2013 were missing baseline CD4, including 5 who died within 6 months.*

Conclusions: With implementation of guidelines to initiate ART at a CD4 ≤350 cells/uL, the mean CD4 count increased among those accessing care to initiate ART, though 6-month mortality remained approximately the same. Despite new guidelines, many participants initiated ART with dangerously low CD4 counts. Earlier HIV diagnosis and rapid linkage to care is necessary to achieve survival gains from new ART guidelines.

1082 HIV Testing of Persons Aged 15–65 Years at Visits to US Physician Offices, 2009–2010

Karen Hoover; Shirley Lecher; Roman Gvetadze; Philip Peters

US Centers for Disease Control and Prevention, Atlanta, GA, US

Background: HIV testing is an important activity of the National HIV/AIDS Strategy. Population estimates of HIV testing in United States are based on self-report and likely overestimate testing rates, yet suggest suboptimal testing coverage. Our objective was to identify missed opportunities for HIV testing at visits to US physician offices.

Methods: We analyzed data from the National Ambulatory Medical Care Survey, which estimates healthcare service provision based on medical record abstractions. We estimated the mean annual number of visits made by persons aged 15-65 years to U.S. physician offices with an HIV test in 2009-2010 by sex, age, race and ethnicity, insurance, and physician specialty. We compared the frequency of HIV testing at visits for preventive care vs. other reasons; symptoms suggestive of acute HIV infection in at-risk populations (fever, malaise, pharyngitis, lymphadenopathy, rash) vs. other reasons; and whether venipuncture was ordered for other laboratory testing.

Results: An HIV test was performed at 4,215,610 visits (0.70%). Women were tested at 2,891,640 visits (0.77%) and men at 1,323,970 (0.58%). As age increased, we found a decreasing trend in HIV testing with testing at 2,299,870 (1.9%) visits by persons aged 15-29 year and 305,170 (0.12%) at visits by those aged 50-65 years ($p<0.001$). Testing was performed at a larger proportion of visits by black (1,200,200 (1.7%)) ($p<0.001$) or Hispanic (786,080 (1.2%)) ($p<0.001$) than white persons (2,056,850 (0.46%)); by persons with Medicaid (876,450 (1.4%)) than private insurance (2,685,300 (0.65%)) ($p=0.031$); and to primary care providers (3,672,610 (1.1%)) than specialists (543,000 (0.20%)) ($p<0.001$). HIV testing occurred more frequently at preventive visits (2,482,170 (2.1%)) than other visits (1,710,200 (0.36%)) ($p<0.001$). Persons who had a visit with symptoms were not tested more frequently. If a blood draw was ordered at a visit, an HIV test was performed more frequently (3,131,580 (2.4%)) compared to a visit without a blood draw (1,084,020 (0.23%)) ($p<0.001$).

Conclusions: HIV testing was performed at only a small proportion of visits to physicians. Many testing opportunities were missed, including during preventive visits, symptomatic visits, and visits where other laboratory testing of blood was ordered. Increased awareness of the recommendation for universal testing, and implementation of structural interventions to facilitate HIV testing along with other laboratory testing, might increase testing coverage.

1083 Frontline Practices With HIV Prevention: A Survey of US Infectious Disease Physicians

Douglas S. Krakower[1]; Susan E. Beekmann[2]; Philip M. Polgreen[2]; Kenneth H. Mayer[1]
Emerging Infections Network
[1]*Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, US;* [2]*University of Iowa, Iowa City, IA, US*

Background: Early initiation of antiretroviral therapy (early ART) for HIV+ patients (pts) and preexposure prophylaxis (PrEP) for at-risk, HIV(-) persons decreases HIV transmission, but little is known about how clinicians implement these strategies. The Emerging Infections Network (EIN), a national network of infectious diseases (ID) physicians, was surveyed in September 2014 to assess practices with early ART, PrEP and other HIV prevention methods.

Methods: An online survey of members assessed intentions and practices with early ART, PrEP, and risk reduction counseling. Analyses were restricted to HIV providers (i.e., treat ≥ 1 HIV+ patient/year). Chi-square tests measured associations between categorical variables.

Results: Almost half (47%) of 1198 members completed surveys; 73% were HIV providers. The sample was regionally diverse; 63% practiced at teaching hospitals, 53% had ≥ 15 years ID experience and 42% treated > 50 HIV+ pts/year. Most providers (87%) said they recommended ART initiation at diagnosis irrespective of CD4 count. However, for pts with CD4 > 500 cells/μL, clinicians would defer ART if a patient was not ready to initiate (97%) or has untreated depression/psychiatric illness (47%) or substance abuse disorder (68%), or if resources for ART/HIV care are limited (50%). For HIV serodifferent couples (SDC), 59% of providers had counseled HIV+ pts about PrEP for partners, 41% had offered visits for partners to discuss PrEP, and 32% had prescribed PrEP. Physicians recommended PrEP when the HIV+ partner is viremic (79%) or aviremic on ART (35%). Respondents supported offering sterile syringes (80%), opiate substitution therapy (68%), and PrEP (42%) to persons injecting drugs, but few felt prepared to provide these (10%, 7% and 26%). Most physicians (78%) provided risk reduction counseling to > 90% of pts newly diagnosed with HIV, yet only 30% did so for established pts. Those with higher volumes of HIV+ pts were more likely to have provided interventions to SDC, including counseling, offering visits to HIV(-) partners, and prescribing PrEP (P <.0001).

Conclusions: ID physicians almost universally recommend early ART, and many have adopted aspects of PrEP provision into practice. However, clinicians may defer ART based on patient readiness or psychosocial factors, and only 1/3 of providers have prescribed PrEP. Interventions that help physicians motivate pts to start ART, identify and overcome missed opportunities to provide PrEP, and routinely deliver risk reduction counseling are needed.

THURSDAY, FEBRUARY 26, 2015

Session P-Y1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Male Circumcision: Risk, Innovation, and Scale-Up

1084 HSV-2 Shedding From Male Circumcision Wounds Among HIV-Infected Men

Mary K. Grabowski[1]; Godfrey Kigozi[2]; Ronald H. Gray[1]; Jordyn L. Manucci[3]; David Serwadda[4]; Eshan U. Patel[3]; Fred Nalugoda[2]; Maria J. Wawer[1]; Thomas C. Quinn[5]; Aaron A. Tobian[3]
[1]*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US;* [2]*Rakai Health Sciences Program, Kalisizo, Uganda;* [3]*Johns Hopkins University School of Medicine, Baltimore, MD, US;* [4]*Makerere University College of Health Sciences, Kampala, Uganda;* [5]*National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, US*

Background: A randomized trial showed that although medical male circumcision (MMC) reduces herpes simplex virus type 2 (HSV-2) acquisition among men, MMC had no impact on HSV-2 transmission to female partners. We conducted a prospective observational study in Rakai, Uganda to assess HSV-2 shedding post-MMC.

Methods: HSV-2 shedding was evaluated among 176 HIV and HSV-2 co-infected men (145 self-reported antiretroviral therapy (ART)-naïve, 9 self-reported ART use with detectable plasma viral load (VL), and 22 self-reported ART with undetectable plasma VL of <400 copies/mL). All men underwent dorsal slit MMC. HSV-2 serostatus was determined by an HSV-2 ELISA (Kalon Biological Ltd, Guilford, UK) with positive serology defined as an optical density index value ≥ 1.5. Preoperative and weekly penile lavages for 6 weeks were tested for HSV-2 shedding and viral load using a real-time quantitative PCR assay with primers to glycoprotein B. HSV-2 shedding was defined as >50 copies of HSV-2 DNA/mL on two separate runs. Prevalence risk ratios (PRRs) and 95%CI were estimated using Poisson regression with generalized estimating equations and robust variance.

Results: HSV-2 shedding was detected in 9.7% (17/176) of men prior to MMC. There was a non-significant increase in the proportion of men with post-MMC HSV-2 shedding relative to baseline at weeks one (12.9%, 22/170, PRR=1.33, 95%CI=0.74-2.38, p=0.329) and two (14.8%, 23/155, PRR=1.50, 95%CI=0.86-2.38, p=0.153). HSV-2 shedding returned to baseline levels by week six after MMC (6.9%, 10/144, PRR=0.71, 95%CI=0.36-1.41, p=0.330). Post-operative HSV-2 shedding did not differ significantly between men who reported ART use compared to those who did not report ART use (PRR=0.67, 95%CI=0.24-1.80). HSV-2 shedding was lower among men with MMC wounds that were certified as healed (PRR=0.61, 95%CI=0.36-1.06, p=0.082). Among men with detectable HSV-2 shedding, the median HSV-2 $\log_{10}$VL/mL was elevated at week one (median=3.2, IQR=2.2-4.8) compared to baseline (median=2.3, IQR=1.8-2.9), though this difference was not statistically significant (p=0.09.) Levels of HSV-2 among men with detectable shedding were similar to baseline at all other post-operative visits.

Conclusions: Penile HSV-2 shedding was non-significantly increased during the first two weeks after MMC. Men undergoing MMC should be counseled on sexual abstinence until wound healing and consistent condom use thereafter.

1085 Association Between Foreskin Microbiota and Local Cytokines in Men From Rakai, Uganda

Cindy M. Liu[1]; Aaron A. Tobian[1]; Jessica Prodger[2]; David Serwadda[3]; Godfrey Kigozi[3]; Fred Nalugoda[3]; Maria J. Wawer[2]; Lance Price[4]; Rupert Kaul[5]; Ronald H. Gray[2]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, US; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]Rakai Health Sciences Program, Rakai, Uganda; [4]Translational Genomics Research Institute, Flagstaff, AZ, US; [5]University of Toronto, Toronto, Canada

Background: Male circumcision (MC) reduces the risk of HIV. Foreskin inflammation induced by specific genital bacteria could elicit local immune responses, promoting inflammation and recruitment of HIV target cells. MC decreases genital anaerobes; however, direct associations between penile microbiota and inflammatory markers have not been demonstrated. We assessed the penile microbiota and cytokine levels in 138 uncircumcised men from Rakai, Uganda.

Methods: Microbiota were characterized using DNA extracted from a coronal sulcus swab eluent by 16S rRNA gene-based qPCR and V3V4 pyrosequencing, obtaining a total of 371,653 sequences. Genital bacteria present at >0.05% of total sequences were included in the analysis. Using the total microbiota density measured by qPCR and microbiota proportional abundance from sequencing, we calculated the microbiota absolute abundance. Eluent levels of 14 cytokines were measured using an electrochemiluminescent detection platform, and correlated with the absolute abundance of genital bacteria using a quasi-Poisson regression model. Model comparisons were performed by chi-square test.

Results: Only IL-8 levels were sufficient to permit quantitative correlation (*Median* = 0.72 $\log_{10}$, *IQR* = 0.18-1.38 $\log_{10}$). Among penile bacteria significantly reduced by MC in prior studies, 11 were positively correlated with IL-8 levels in univariate analyses, including *Prevotella*, *Porphyromonas*, *Finegoldia*, *Peptoniphilus*, *Peptostreptococcus*, *Anaerococcus*, *Dialister*, *Mobiluncus*, *Actinomyces*, *Sutterella*, and Unclassified Clostridiales Family XI. In multivariate analysis *Prevotella* (Δ= +49.6% in IL-8 per 10-fold increase in *Prevotella spp*, *P*=0.048) and *Peptostreptococcus* (Δ= +34.0%, in IL-8 per 10-fold increase, *P*<0.001) abundances were associated with increased IL-8 levels, with a similar trend for *Staphylococcus* (Δ= +21.5%, *P*=0.062). In contrast *Corynebacterium*, which are increased post-MC, were associated with lower IL-8 levels (Δ= -22.8%, *P*=0.0058).

Conclusions: *Prevotella* and *Peptostreptococcus*, which are decreased by MC, were associated with significant increases in penile IL-8, while *Corynebacterium*, which increases post-MC, was associated with lower IL-8. These findings suggest that post-MC changes in microbiota may reduce inflammatory cytokines and HIV susceptibility.

1086 Mobile VMMC Teams in Tanzania See Older Clients and Have Higher Followup Rates

Augustino M. Hellar[1]; Dorica Boyee[1]; Hally Mahler[1]; Marya Plotkin[1]; Touma Ng'wanakilala[1]; Kelly Curran[2]; Tigistu Ashengo[2]; Hawa Mziray[1]; Erick Mlanga[3]; Sifuni Koshuma[4]

[1]Jhpiego, Dar es Salaam, United Republic of Tanzania; [2]Jhpiego, Baltimore, MD, US; [3]US Agency for International Development, Dar es Salaam, United Republic of Tanzania; [4]Ministry of Health and Social Welfare, Iringa, United Republic of Tanzania

Background: Tanzania has rolled out Voluntary Medical Male Circumcision (VMMC) since 2009 in 12 priority regions with high HIV and low male circumcision rates. More than 390,000 clients have been served in Iringa, Njombe and Tabora regions with support from Jhpiego and USAID. Nearly 80% of clients reached are aged 10-19 years. Iringa and Njombe are approaching their original 80% coverage target. Service delivery modalities include routine, in which services are delivered in larger health facilities, typically at low volume, and campaigns where teams of providers move into new communities and do 1-3 week bursts of intense, high-volume provision of services. In May 2014, mobile services were introduced specifically to serve the hard-to-reach clients not reached by other modalities. This roving team of providers, move along villages to provide VMMC services even in non-facility settings. The analysis presents findings on differences in the three modalities.

Methods: Secondary data review was conducted on 148,880 individual records, stripped-of identifiers from all three regions from October 2013-August 2014, the year when mobile teams were introduced. Records were broken into three modalities: campaign, routine and mobile. Frequencies were compared between the modalities and Chi^2 was used to test for the significance of the differences.

Results: 76% of the 148,880clients circumcised during the year were aged <20 years. Mobile teams reached older clients compared to other service delivery modalities (p<0.001), as shown below.

Overall HIV testing uptake was high (97%) regardless of the modality. A higher proportion tested HIV positive in the routine followed by mobile modalities (2.1% and 1.4% respectively). Follow-up rates were significantly higher in the mobile modality both for 1st and 2nd visits (91.7% and 63.1% respectively) compared to static modality (70% and 36% respectively); p-value < 0.001).

Service Modality	No. of clients served	% of clients < 20 years	% of Clients ≥ 20 years
Campaign	132,080	78%	22%
Routine	11,392	71%	29%
Mobile	5,408	62%	38%
Total	148,880	76%	24%

Conclusions: A higher proportion of older clients (20 years or older) accessed VMMC services through mobile teams compared to other modalities. Mobile teams are circumcising in lower volume settings than campaigns where it's easier to offer more privacy to older clients. Introduction of mobile teams could be an efficient strategy to attract older clients who have not previously accessed services. With the slightly high proportion of HIV positive clients, linkage to care and treatment must be ensured. Follow-up rates were very high in the mobile setting, probably because of active client follow-up.

1087 High Acceptability of PrePex™ Device in Routine Programmatic Settings in Rwanda

Eugene Rugwizangoga[1]; Beata Mukarugwiro[1]; Jovite Sinzahera[1]; Alphonse Mutabaruka[1]; Gloriose Abayisenga[1]; J.D. Ntakakirabose[1]; Ngeruka Leon[4]; Eugene Zimulinda[3]; Kelly Curran[2]; Tigistu Ashengo[2]

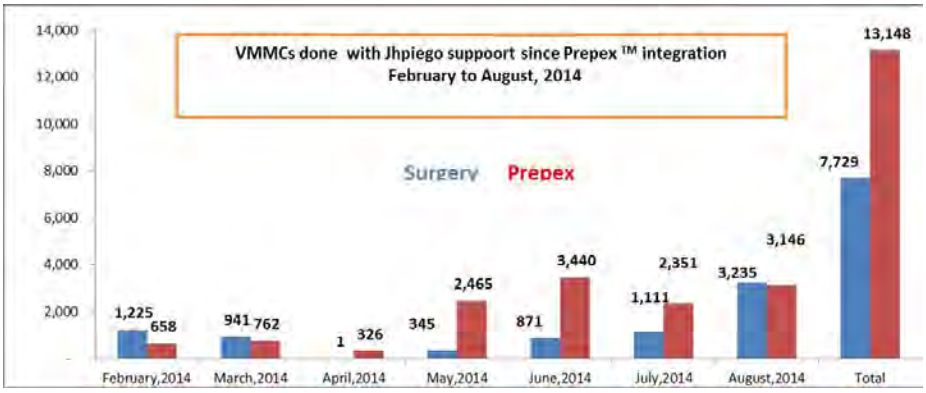
[1]Jhpiego/Rwanda, Kigali, Rwanda; [2]Jhpiego, an Affiliate of Johns Hopkins University, Washington, DC, US; [3]US Department of Defense, Rwanda, Kigali, Rwanda; [4]Rwanda Military Hospital, Kigali, Rwanda

Background: The PrePex™ device offers an alternative to conventional surgical methods of male circumcision. Because it does not require injectable anesthesia or the cutting of vital tissue, PrePex™ requires less surgical capacity and may be more acceptable to men, potentially increasing uptake of this proven HIV prevention intervention. In May 2013, PrePex™ received WHO prequalification for adults aged 18 and above. Rwanda was the first country to conduct PrePex™ safety and acceptability studies and is now the first to scale-up PrePex™ in programmatic settings. PrePex™ currently comes in five adult sizes, A through E. Since 2009, Jhpiego, with PEPFAR funding through the US Department of Defense, has supported the Rwanda Defense Force (RDF) to provide VMMC to soldiers, their dependents and civilians living near base clinics. Since February 2014 PrePex™ has been offered alongside conventional surgery to adult VMMC clients at Jhpiego-supported RDF sites.

Methods: We reviewed routine program data from Jhpiego-supported RDF sites from program inception in October 2009 through August 2014.

Results: Between October 2009 and August 2014 86,284 adolescent boys and adult men were circumcised at Jhpiego-supported RDF sites, with 20,877 of these clients served in the seven months since PrePex™ was added. Since PrePex™ was introduced nearly two thirds of circumcisions have used the device, with 13,148 (63%) of clients receiving PrePex™

and 7,729 (37%) conventional surgery. Overall uptake has been increasing year to year; the number of clients served doubled from 2012 to 2013 thanks to efficiency approaches such as task shifting to nurses and use of mobile (outreach) teams. PrePex™ introduction appears to have accelerated this trend although in July 2014 the program experienced device stockouts especially in sizes A,D and E.



PrePex™ and Surgical VMMCs Conducted at Jhpiego-supported RDF Sites, Feb-Aug 2014

Conclusions: The introduction of the PrePex™ device in routine programmatic settings is well accepted by adult VMMC clients in Rwanda, with 63% of this age group choosing PrePex™. The acceptance rate would have likely have been higher if not for a stock out of PrePex™ devices beginning in July 2014. Programs planning to scale up PrePex™ should anticipate the supply chain implications of this device which is currently available in five adult sizes.

1088 Self-Selection of Circumcision Acceptors, Risk Compensation and Effectiveness of Circumcision Among Service Recipients, Rakai, Uganda

Joseph Kagaayi[1]; Xiangrong Kong[2]; Godfrey Kigozi[1]; Fred Nalugoda[1]; Steven J. Reynolds[3]; David Serwadda[4]; Nelson K. Sewankambo[5]; Maria J. Wawer[2]; Ronald H. Gray[2]

[1]Rakai Health Sciences Program, Entebbe, Uganda; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [3]Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, US; [4]Makerere University School of Public Health, Kampala, Uganda; [5]Makerere University College of Health Sciences, Kampala, Uganda

Background: There are limited data on characteristics of acceptors of safe male circumcision (SMC), risk compensation and effectiveness of SMC service programs. We compared baseline characteristics of SMC acceptors and non-acceptors, determined the effectiveness of SMC and compared trends in sexual behaviors of the two groups using data on men aged 15-49 years enrolled in the Rakai community cohort study in Uganda.

Methods: 1192 non-Muslim HIV-negative SMC acceptors were compared to a stratified random sample of 2384 uncircumcised men. Baseline behaviors and trends over time were compared using multivariable modified Poisson with generalized estimating equations. HIV incidence rates between the groups were compared using the incidence rate ratio (IRR) from a multivariable Poisson regression model.

Results: Overall SMC acceptors were younger, less likely to be currently or previously married, and had higher education attainment. Among sexually active men, baseline sexual behaviors were comparable between the groups. However SMC acceptors had 26 percent higher prevalence of genital ulcers compared to non-acceptors (p=0.025). After circumcision, the rate of increase in prevalence of sexual activity was 2.6 percent higher among SMC acceptors (p<0.001) compared to non-acceptors. On stratification by age, the difference was 3.2 percent higher, p=0.08 among youths (15-24) but no difference was seen above 24 years. The prevalence of sexual activity with women in higher risk occupations (bar attendants, alcohol brewers, restaurant workers, itinerant traders, fisher folk, housemaids), increased by 10.2 percent per year among SMC acceptors (p=0.007) but no change occurred among uncircumcised men. Trends in other sexual behaviors were similar between the groups. HIV incidence among SMC acceptors was 0.61/100 person years and 1.11/ 100 person years among non-acceptors (adj. IRR=0.50, p=0.05, 95 percent CI=0.25-1.01).

Conclusions: The higher prevalence of genital ulcers among sexually active SMC acceptors suggests that higher risk sexually active men self-selected to receive SMC. The suggestion of faster increase in sexual activity among circumcised youths and the increase in partnerships with higher risk women suggest possible behavioral disinhibition and need to be investigated in other settings. Though these behaviors, did not attenuate the effectiveness of SMC, there is need to add avoidance of high risk partners to the current SMC messaging.

1089 Potential Protection From HIV Transmission by Penile Cuttings in Papua New Guinea

Ivy H. Shih[1]; Lester Asugeni[2]; Matthew David[5]; Paul Horwood[5]; Parana Hewage Mangalasir[3]; David Mc Laren[3]; Rachael Tommbe[2]; Andrew Vallely[1]; Arnold Waine[4]; Stuart G. Turville[1]

[1]The Kirby Institute, Sydney, Australia; [2]Pacific Adventist University, Port Moresby, Papua New Guinea; [3]James Cook University, Cairns, Australia; [4]University of Papua New Guinea, Port Moresby, Papua New Guinea; [5]Papua New Guinea Institute of Medical Health, Goroka, Papua New Guinea

Background: Male circumcision reduces HIV acquisition by 66% but there has yet to be a scientific consensus on the protective mechanism. Current hypotheses implicate the inner foreskin due to a thinner primary barrier and greater target cell density. Unique to Papua New Guinea (PNG), ethnographic studies documented widespread non-medical penile cutting practices. The dorsal slit (DS) is the most common and leads to exposure of glans and inner foreskin and provides an opportunity to study a scenario where the inner foreskin is exposed but not removed. We present results from a cohort study assessing histological changes to thin skin that may aid prevention in both circumcised and dorsal slit men.

Methods: Foreskin samples were obtained from men with or without existing DS following elective enrolment at a free circumcision service offered at Port Moresby, PNG. Histological evaluation on frozen and paraffin embedded foreskin sections assessed primary barrier parameters that potentially afford HIV protection. Phenotypes were measured on hematoxylin and eosin stained sections: Stratum corneum thickness (SC), epithelial surface area (SA) and epithelial adhesion to the dermis, the latter two used to evaluate foreskin fragility. Alkaline expansion was conducted to representatively measure SC architecture. Imaging with a high- resolution slide scanner generated an entire tissue section image and epithelium SA was quantified with a recognition algorithm. Density and distribution of HIV target cells foreskin tissue was determined by immunofluorescence to establish foreskin vulnerability.

Results: Men with DS had significantly thicker SC in their inner foreskin than uncircumcised men: 12.09um±2.92 versus 9.87um±2.54 respectively (n=16; p<0.001; 500 total measurements). In DS individuals, the inner and outer foreskin epithelium SA collectively showed significant difference (outer: 0.0457±0.0108mm^2; inner:0.0285±0.0078mm^2) (p<0.001; 160 total measurements)). This observation was shared with epithelium-dermis adhesion (outer: 2.4583±0.7891;inner: 1.7878±0.5510) (p<0.01). CD4 T cells were also observed in the inner and outer foreskin.

Conclusions: The DS confers a degree of protection due to the inner foreskin SC thickening similar to the protective thick skin SC phenotype of outer foreskin. Beyond the protective primary barrier, the increased fragility of the inner foreskin in comparison to outer foreskin presents a new parameter that may account for the inner foreskin being a more vulnerable area.

WEDNESDAY, FEBRUARY 25, 2015

Session P-Y2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Linkage to Care and ART Initiation

1090 Linkage to HIV Care Following Home-Based Testing and CD4 in Rural Malawi

Sophie Masson[1]; Jihane Ben Farhat[1]; Charles Masiku[4]; Benson Chilima[2]; Elisabeth Szumilin[3]; Leon Salumu[3]; Jean-François Etard[1]; **David Maman**[1]

[1]Epicentre/Médecins Sans Frontières, Paris, France; [2]Ministry of Health, Lilongwe, Malawi; [3]Médecins Sans Frontières, Paris, France; [4]Médecins Sans Frontières Malawi, Lilongwe, Malawi

Background: HIV diagnosis and linkage to care are critical steps along the HIV continuum of care. We assessed HIV-positive status awareness and subsequent linkage to care of the newly diagnosed in a representative sample of Chiradzulu, Malawi, after 10 years of ART scale-up.

Methods: A nested cohort study within a population-based survey of persons aged 15 to 59 years old was conducted between February and May 2013. During the survey, each consenting participant was interviewed and tested for HIV. Individuals found to be HIV positive had their CD4 tested at home using a point of care test. Those who were unaware of their status were included in the nested cohort study. Linkage to HIV care was defined as attending HIV care within 3 months of HIV diagnosis among newly diagnosed individuals. Among all HIV-positive, a logistic model explored factors associated with status awareness prior to the survey. Then, among the newly diagnosed, a Weibull model was fitted to explore factors associated with linkage to care.

Results: Among the 8,277 individuals eligible for the survey, 7,270 were included and tested for HIV. A total of 1,233 participants were found to be HIV-positive, corresponding to an overall prevalence of 17.0% (95%CI 16.1-17.9). Prevalence was higher among women than men (19.7% vs 13.0%, p<0.01). Among HIV-positive individuals, 77.0% (95%CI 74.4-79.3) were aware of their status and 72.8% (95%CI 70.1-75.3) in care. In the multivariate analysis, women and older people were more likely to be aware of their diagnosis.

Among the newly-diagnosed, linkage to care occurred most frequently during the first weeks after diagnosis. The linkage probabilities after 2 weeks, 1 month and 3 months were 30.3%, 36.5% and 47.5%, respectively. In multivariate analysis, older persons (40-59vs15-29, aHR 3.39, 95%CI 1.83-6.26, p<0.01), women (vs men, aHR 1.73, 95%CI 1.12-2.67, p<0.01) and those in need of ART (vs those not in need, aHR 1.61, 95%CI 1.03-2.52, p=0.04) were more likely to link to care after diagnosis.

Table: **Multi-variable Weibull model exploring risk factors associated with linkage to HIV care following an HIV diagnosis through HBTC, Chiradzulu District, Malawi, 2013. (N=244)**

Factors		Number of patients newly diagnosed	Rate of linkage/100 person-months (95% CI)	Adjusted HR (95% CI)	*p-value*
Gender					
	Men	108	20.9 (15.6-28.0)	1	
	Women	136	28.8 (22.8-36.4)	1.73 (1.12 – 2.67)	0.01
Age groups					
	15-29	75	14.5 (9.8-21.4)	1	
	30-39	99	28.3 (21.4-37.3)	2.14 (1.23 – 3.73)	0.01
	40-59	70	36.8 (27.0-50.1)	3.39 (1.83 – 6.26)	<0.01
ART Eligible					
	No	125	21.2 (16.2-27.7)	1	
	Yes	119	29.8 (23.2-38.2)	1.61 (1.03 – 2.52)	0.04
Total		244	25.1 (20.9-30.1)		

Conclusions: Half of newly diagnosed individuals had linked to care in the three months following home based testing and CD4 assays in a population where three quarters of HIV-positive persons were already on care. It provides new evidence that a large proportion of the HIV-positive population can be on care in sub-Saharan Africa. Men and younger individuals were less likely to be diagnosed and less likely to link to care after diagnosis. New testing and linkage to care strategies should target these groups.

1091 Rapid ART Initiation Reduces Loss Between HIV Testing and Treatment: The RapIT Trial

Sydney Rosen[1]; Mhairi Maskew[2]; Matt P. Fox[1]; Cynthia Nyoni[2]; Constance Mongwenyana[2]; Given Malete[2]; Ian Sanne[2]; Julia K. Rohr[1]; Lawrence Long[2]

[1]Boston University, Boston, MA, US; [2]University of the Witwatersrand, Johannesburg, South Africa

Background: Very high rates of patient attrition from HIV care between HIV testing and ART initiation have been documented in sub-Saharan Africa. Accelerating the steps required for ART initiation has been proposed as a way to reduce attrition and achieve earlier treatment initiation.

Methods: The RapIT randomized controlled trial evaluated the effect of immediate ART initiation on ART uptake in two public sector clinics in South Africa. Adult, non-pregnant patients receiving a positive HIV test or first CD4 count were randomized to standard or immediate (rapid) initiation. On the day of HIV test or first CD4 count, patients in the rapid arm received a point-of-care CD4 count if needed; those ART eligible then received a rapid TB test if symptomatic, rapid blood tests, physical exam, accelerated education

and counseling, and ARV dispensing. Rapid procedures were conducted by nurses and counselors comparable to clinic staff. Patients in the control arm followed standard clinic procedures (3-4 clinic visits over 2-4 weeks prior to ARV dispensing). Here we report ART uptake and early retention ≤1 month of ART initiation.

Results: Enrollment was completed in August 2014. 172 patients were randomized to rapid and 181 to standard initiation. There were no important differences between arms in gender, age, or CD4 count at study enrolment. In both arms, 83% of patients newly diagnosed with HIV were already eligible for ART. In the rapid arm, 97% (139/143) of patients eligible for ART initiated treatment ≤1 month, including 73% on the same day as study enrollment and 19% ≤1 week. In the standard group, 57% (86/151) initiated ≤1 month (hazard ratio for ART uptake=1.69; 95%CI 1.47-1.95). All those who did not initiate ≤1 month in the rapid arm (n=5) were required to delay ART for TB treatment. Time used for treatment initiation, from study enrollment to dispensing, averaged 2.8 hours for rapid arm patients not requiring TB testing. Within 1 month of initiation, 86% (n=120) of rapid arm and 85% (n=112) of standard arm patients had attended the clinic for their first follow-up visit. Of 54 subjects with ≥6 months follow-up and documented viral load, 91% and 77% were virally suppressed in the rapid and standard arms respectively.

Outcome	Standard arm*	Rapid arm	Risk difference [95% CI]	Crude relative risk [95% CI]
Initiated ART ≤ 28 days (n (%))	86 (57%)	138 (97%)	0.40 [0.31-0.48]	1.69 [1.47-1.95]
Median (IQR) days to outcome	15 (10-21)	0 (0-0)	-	-
Initiated ART ≤ 90 days	110 (73%)	139 (97%)	0.24 [0.17-0.32]	1.33 [1.21-1.48]
Median (IQR) days to outcome	18 (12-25)	0 (0-1)	-	-
Attended follow up visit ≤ 1 month of treatment initiation	95 (85%)	120 (86%)	-0.01 [-0.08-0.10]	1.01 [0.91-1.12]
Median (IQR) days to outcome	28 (28-28)	28 (25-28)	-	-
Suppressed HIV viral load ≤ 180 days of treatment initiation	17/22 (77%)	29/32 (91%)	0.13 [-0.07-0.34]	1.17 [0.91-1.51]
Median (IQR) days to outcome	168 (165-196)	193 (168-222)	-	-
Missing viral load result	20/42 (48%)	29/61 (48%)	-	-

*Reference group for risk difference and relative risk estimations

Outcomes and Relative Risks by Study Arm

Conclusions: Immediate ART initiation reduces loss of patients between treatment eligibility and treatment initiation significantly and is feasible and acceptable in a public health clinic setting. It should be considered for adoption in high-volume clinics in the public sector in Africa.

1092 Outcomes of a Clinic-Health Department "Data to Care" Relinkage Intervention

Joanna M. Bove[2]; Matthew R. Golden[2]; Shireesha Dhanireddy[2]; Robert Harrington[2]; Julie Dombrowski[2]

[1]*University of Washington, Seattle, WA, US;* [2]*University of Washington, Seattle, WA, US*

Background: The effectiveness and best structure of programs to identify out-of-care persons with HIV and relink them to care is uncertain. We implemented and evaluated an HIV care relinkage intervention that uses both clinical and health department surveillance data.

Methods: The intervention occurs in the Madison Clinic, a university affiliated, Ryan-White funded clinic in Seattle, WA. The program uses a clinic registry to identify persons who are potentially out of care. The registry collates data from electronic health records, intake forms, and case management databases. HIV+ patients are eligible for relinkage outreach if they completed ≥1 clinic visit in the last 1000 days but no visits for ≥12 mo. A linkage specialist (LS) investigates cases and conducts outreach with the goal of care relinkage. We analyzed LS outreach success over a 12 mo. observation period among patients identified for outreach on 11/1/12 (intervention cohort). We compared outcomes of this cohort to patients who would have met criteria for the intervention one year prior to its initiation (historical cohort). We used c^2 tests and logistic regression to compare the percent relinked and the mean time to relinkage between cohorts.

Results: 753 patients were identified as out of care on 11/1/12. Matching with surveillance data determined that almost half (347 [46%]) of these patients had moved, transferred care or were incarcerated (ineligible). LS investigations determined that an additional 245 (33%) were ineligible. Of the 161 (21%) truly out of care patients, 40 (25%) relinked before LS contact. Of the remaining 121, 38 (31%) did not have contact information; 46 (38%) did not respond to contact attempts; and 37 (31%) were successfully contacted, of which 20 (54%) relinked. In all, 116 (15%) intervention cohort patients relinked to care in 12 months; 24 (21%) were among the LS attempted contacts. 48 (42%) of the patients who relinked were initially identified as ineligible, but transferred back to Madison or were released from incarceration. More patients in the intervention cohort than the historical cohort relinked (15% vs. 10% [RR=1.6 (1.2-2.1)]), and they had a shorter mean time to relinkage (4.8 vs. 6.3 mo.; p=0.001).

Conclusions: This collaborative HIV clinic-health department relinkage intervention showed modest ability to identify and return out-of-care patients to care compared to historical controls and highlights the utility and efficacy of integrating clinical and surveillance data in relinkage efforts.

1093 HIV Partner Services Can Achieve Near-Universal Linkage to HIV Care

David A. Katz[1]; Julia C. Dombrowski[1]; Susan E. Buskin[2]; Amy Bennett[2]; Elizabeth A. Barash[2]; Matthew R. Golden[1]

[1]*University of Washington, Seattle, WA, US;* [2]*Public Health - Seattle & King County, Seattle, WA, US*

Background: Timely linkage to care following HIV diagnosis is necessary for maintaining the health of persons living with HIV and realizing the secondary prevention benefits of antiretroviral therapy and behavior change. HIV partner services (PS) provide an opportunity not only to test exposed partners but also to facilitate timely linkage for persons with newly diagnosed HIV infection (index cases).

Methods: In King County, WA, PS staff attempt to provide PS to all persons newly diagnosed with HIV infection. PS are designed to ensure that index cases link to care and that partners are notified and tested. PS staff do not close cases until they have verified that index cases have linked to care. Using HIV surveillance and PS data, we examined the impact of receiving PS on timely linkage to care, defined as first CD4 count or HIV viral load (VL) within 3 months of initial HIV diagnosis, using chi-squared tests and logistic regression.

Results: From 2010-2013, 1043 persons aged 15 and older were newly diagnosed with HIV infection in King County, of whom 963 (92%) linked to care within 3 months and 999 (96%) within 1 year. Only 18 (1.7%) did not have ≥1 CD4 or VL reported to surveillance by 9/8/2014. Of 1043 new cases, 838 (80%) received PS, 250 (30%) of whom were interviewed during a public health program called One-on-One, which provides patients with counseling and an initial clinical assessment, including CD4 and VL testing. PS recipients were more likely to link to care within 3 months than non-recipients (94 v. 84%, p<.001); this association persisted even when One-on-One clients were excluded from the analysis (93 v. 84%, p<.001). In multivariable analysis, receiving PS remained significantly associated with timely linkage to care (p<.001); sex, gender of partners, age, diagnosing provider type, and year of diagnosis were not associated with timely linkage. Men who have sex with men (MSM), who represented 814 (78%) of cases during the study period, were more likely to receive PS than non-MSM (82 v. 74%, p=.009) but had identical levels of timely linkage to care (92 v. 92%, p=.9).

Conclusions: Identifying linkage to care as an explicit outcome for HIV PS can increase timely linkage to care among persons newly diagnosed with HIV infection and has achieved nearly universal linkage to HIV care in King County, WA.

1094 Immunodeficiency at the Start of ART: A Global View

Klea Panayidou[1]; Ole Kirk[3]
On behalf of the IeDEA Collaboration and the COHERE Collaboration
[1]*University of Bern, Bern, Switzerland;* [2]*Université Victor Segalen Bordeaux 2, Bordeaux cedex, France;* [3]*University of Copenhagen, Copenhagen, Denmark*

Background: Early initiation of antiretroviral therapy (ART), at higher CD4 counts, prevents disease progression and reduces sexual transmission of HIV-1. We describe the CD4 count at the start of ART for five continents.

Methods: Data are from the International epidemiologic Databases to Evaluate AIDS (IeDEA) from North America, the Caribbean, Central and South America, Asia-Pacific and West, Central, East and Southern Africa and from the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE). Patients aged >=16 years with known sex were eligible. Analyses were stratified by World Bank country classification (as of 01/2013) and sex. CD4 counts were multiply imputed (50 imputations). Weighted additive mixed models were used to smooth aggregated median CD4 counts over the years per income group, country and sex. Fitted / predicted CD4 counts were aggregated using Rubin's rules.

Results: 747,684 patients from 42 countries were included in the analysis: 47,155 from North America (2 countries), 15,738 from the Caribbean, Central and South America (7), 3,066 from Asia Pacific (2), 539,064 from sub-Saharan Africa (19) and 142,661 from Europe (12). Trends in median CD4 counts at start of ART from 2002, when ART was scaled up globally, were similar in low-income and upper middle-income countries (table). Overall, median counts were slightly higher in lower middle-income and highest in high-income countries. All countries except the United Republic of Tanzania (171 cells/μL) reached median CD4 counts >=200 cells/μL. Six countries reached counts >=350 cells/μL: Australia; Belgium; France; Sweden; Switzerland; United States. In all except high-income countries, median counts were higher and increased to a greater extent in women than men.

	Low-income		Lower middle-income		Upper middle-income		High-income	
No. of patients	139,549		183,767		105,873		166,580	
No. of countries	14		6		7		15	
Median year of starting cART	2009		2008		2009		2005	
Median age	36		35.3		34.7		38.9	
% women	64%		62%		64%		24%	
Median CD4 cell count (cells/μL)	Male	Female	Male	Female	Male	Female	Male	Female
2002	63	78	89	113	93	110	200	209
2004	82	101	102	129	104	123	198	206
2006	105	130	117	148	115	137	219	223
2008	129	161	134	170	131	155	262	258
2010	154	193	153	195	158	188	308	295
2011	168	211	163	209	179	213	327	310
2012	182	230	174	223	205	243	342	321
2013	198	250	186	238	235	280	355	330
Change 2002 - 2013	+135	+172	+172	+126	+142	+170	+155	+122
Overall 2002 - 2013 (Male & Female)	136		146		139		249	

Conclusions: Median CD4 count at start of ART increased in most countries, but remained below 350 cells/μL in all low- and middle-income countries in 2013. Substantial effort and resources are needed to achieve earlier implementation of ART globally.

1095 Providers' Attitudes and Practices Related to ART Use for HIV Care and Prevention

Kate Buchacz[1]; Jennifer Farrior[2]; Gheetha Beauchamp[3]; Laura McKinstry[3]; Ann Kurth[4]; Barry S. Zingman[5]; Fred Gordin[6]; Deborah Donnell[3]; Wafaa M. El-Sadr[7]; Bernard M. Branson[1]
[1]*US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US;* [2]*FHI360, Durham, NC, US;* [3]*Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US;* [4]*New York University School of Medicine, New York, NY, US;* [5]*Montefiore Medical Center and Albert Einstein College of Medicine, New York, NY, US;* [6]*Veterans Affairs Medical Center and George Washington University, Washington, DC, US;* [7]*Columbia University and Harlem Hospital, New York, NY, US*

Background: HPTN 065 examined the feasibility of an enhanced Test, Link to Care, plus treat (TLC-plus) approach for HIV prevention in the Bronx, NY and Washington, DC. We surveyed ART-prescribing providers in the two jurisdictions twice to assess temporal changes in knowledge, attitudes and practices pertaining to early initiation of ART over the 3-year study period, during which DHHS guidelines evolved to recommend universal ART for HIV-infected persons in the U.S.

Methods: All ART-prescribing providers (including physicians, nurse practitioners, physician assistants, and residents/fellows) at 39 participating HIV care sites were asked by email to complete an anonymous web-based survey with a nominal incentive upon survey completion. The survey was administered at baseline (9/2010-5/2011) and follow-up (5/2013-12/2013). Baseline and follow-up data were not linked by respondent. We used t-tests and Kruskal-Wallis tests to assess for statistical differences in distribution of responses across the two surveys.

Results: We analyzed data from 165 providers at baseline and 141 providers at follow-up (survey response rates of 57% and 53%, respectively). In both surveys, almost 60% of respondents were female; median age was 46 years; about 60% were white, two-thirds were physicians, and nearly 80% considered themselves HIV specialists. The percentage of providers who reported recommending ART initiation irrespective of CD4 cell count increased from baseline to follow-up (15% vs. 68%, $p<0.01$) as did the percentage who would initiate ART earlier for patients having unprotected sex with partners of unknown HIV status (64% vs. 82%, $p<0.01$) and for those in HIV-discordant sexual partnerships (75% vs. 87%, $p<0.01$). The percentage of providers who strongly agreed with the statement "Early initiation of ART can slow the spread of HIV in a community by making patients less infectious to others" also rose (65% to 88%, $p<0.01$). Providers reported initiating more patients on ART in the past year with the main goal of making it less likely that patients would transmit HIV to their sexual partners (median of zero vs. three patients, $p<0.01$).

Conclusions: From 2011 to 2013, a greater percentage of ART-prescribing providers in the two jurisdictions supported initiating ART for all HIV-infected patients and using ART to prevent transmission, consistent with new scientific evidence and changes in HIV treatment recommendations during the conduct of HPTN065.

WEDNESDAY, FEBRUARY 25, 2015

Session P-Y3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

HIV Testing: Innovations and Scale-Up

1096 Availability and Quality of Online HIV Self-Test Kits in China and the United States

Fengying Liu[2]; Larry Han[3]; **Weiming Tang**[1]; Shujie Huang[2]; Ligang Yang[2]; Heping Zheng[2]; Bin Yang[2]; Joseph Tucker[1]

[1]University of North Carolina, Guangzhou, China; [2]Guangdong Provincial STD Control Center, Guangzhou, China; [3]University of North Carolina, Chapel Hill, NC, US

Background: Among people living with HIV, at least 20 % in the US and the majority worldwide are unaware of their serostatus. HIV test uptake remains sub-optimal, and HIV self-testing (HIVST) represents one way of expanding test uptake. The advent of large e-commerce websites in China and the United States provide a large, scalable platform for selling HIV self-test (HIVST) kits. The goal of this study was to investigate the availability and self-reported quality of HIVST kits on major e-commerce websites in China and the US.

Methods: In 2013, two trained public health professionals systematically examined the availability and self-reported quality of online HIVST kits. We chose the largest e-commerce websites based on annual retail sales in China (Taobao, Jingdong) and the US (Amazon, Ebay). The number of kits sold, number of comments, test method, linkage to care, counseling personnel quality, and prices were collected through websites. HIVST counseling personnel quality included self-reports of medical training and pervious HIV counseling experience. Medical training was defined as an undergraduate degree in the health sciences or substantial training course from a medical institute.

Results: We identified a total of 43 vendors that sold 38 brands of HIV self-testing kits. All Chinese brands were approved by the Chinese State Food and Drug Administration (SFDA) and 30/35 US brands were approved by the US FDA. In China and the US, all HIVST kits were sold by private companies. No Chinese vendors and only 37% (13/35) of US vendors provided HIV confirmatory testing service together with referral services. All seven Chinese and 46% (16/35) of American vendors provided general advice directing individuals to the local public health authority without specific hotline or address information. In terms of HIVST counseling, all vendors had generic customer service available, but HIVST counseling quality was poor. Only 28% (2/7) and 17% (6/35) of Chinese and US customer service employees had medical training, respectively. None of Chinese and 11% (4/38) of US customer service employees had prior counseling experience with HIV-infected individuals.

Conclusions: Empirical data on linkage to care and retention in care through these HIVST systems would be useful. Ecommerce may improve uptake of HIVST, but current models driven by the private sector do not fully realize the potential of this opportunity.

1097 Home HIV Testing and Medical Care: Doing the Right Thing

Charulata J. Sabharwal; Sharmila Shah; Chi-Chi N. Udeagu

New York City Department of Health and Mental Hygiene, Queens, NY, US

Background: HIV testing is the initial, critical step for people with HIV into the continuum of care. The approval of the home test in 2012 addressed this by expanding accessibility of HIV testing to groups who do not test in traditional venues. However, concerns have been raised over the home test's cost (39.99USD), uptake, and users' willingness to seek confirmatory testing.

Methods: The New York City (NYC) Health Department offers partner services and linkage to care to all persons newly diagnosed with HIV city-wide. Since 2013, home test use has been systematically collected among all such persons assigned for partner services. We analyzed demographic and behavioral characteristic data among men who have sex with men (MSM) who home tested compared to MSM who did not report home testing from January 2013 - July 2014.

Results: Of the 2084 MSM assigned, 53 (2.5%) reported the use of a home test. The median age (32 years) did not differ between home test users and non-users. MSM home test users were more likely to be white (43% vs. 25%) and less likely to be black (23% vs. 37%) or Hispanic (23% vs. 31%) compared to non-users. Compared to MSM who did not home test, MSM home test users were more likely to have attended college/graduate school (71% vs. 48%, p=0.002) or test HIV negative within the past 12 months (83% vs. 62%, p=0.002). Furthermore, home testers had a lower rate of incarceration (4% vs. 9%, p=0.04). Of the 53 who home tested, 27 (51%) reported testing preliminary positive on the home test. Timely linkage to HIV care (within 3 months) after diagnosis did not differ between home test users and non-users (63% vs. 69%).

Conclusions: We demonstrate that among high-risk MSM in NYC, many home test users were routine testers as opposed to infrequent or never testers. This finding suggests that the current market for such tests includes persons who already test in traditional venues but may also choose to test at home. Importantly, MSM home-testing preliminary positive sought medical attention for confirmatory testing and linkage to care. The lower uptake among MSM of color compared to white MSM will require further investigation but may reflect socioeconomic differences. To address issues relating to the current cost, the NYC health department offers home test kits to HIV exposed partners who decline testing in traditional settings. Wider home testing for some risk groups may require free or lower cost kits.

1098 Using Grindr™, a Social-Media–Based Application, to Increase HIV Self Testing Among High-Risk Men Who Have Sex With Men in Los Angeles, California, 2014

Alexandra Medline[1]; Emily Huang[2]; Robert Marlin[2]; Sean D Young[2]; Justin Kwok[2]; Jeffrey D. Klausner[2]

[1]McGill University, Toronto, Canada; [2]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, US

Background: In the United States, African American and Latino men who have sex with men (MSM) have the highest incidence of HIV infection, burden of HIV/AIDS, and about one of four are unaware of their infection. The recently FDA approved OraQuick® In-Home HIV self-test kit, in combination with an Internet-based test request system, might help reduce common barriers for testing, including poor access, stigma, and if provided for free, cost.

Methods: An advertisement publicizing free HIV self-test kits targeting high-risk HIV incidence areas in Los Angeles was placed on Grindr™ from April 17 to May 29, 2014. Users were linked to http://freehivselftests.weebly.com/ to choose a method of self-test delivery: U.S mail, a Walgreens® voucher, or from a vending machine. We invited eligible users to take a survey on testing experiences. Eligible participants were African American or Latino, MSM, and > 18 years of age. UCLA IRB approved the study protocol.

Results: During the campaign, the website received 11,939 unique visits (average: 284 per day) and 344 test requests. Of those 344, 230 (67%) were requests for mailed tests, 101 (29%) were for vouchers, and 13 (4%) were to use the vending machine. Of the 121 eligible study participants, 38% were between the ages of 18-30, 14% were African American, 86% were Hispanic/ Latino, 68% reported condomless anal sex in the past 3 months, 38% had only tested once in the past year, and 11% had never tested. Of the 63 surveyed respondents, 54 (95%) of 57 reported using the test was easy; 55 (96%) reported testing HIV negative, and two (4%) reported testing HIV positive. Both persons with positive test results sought confirmatory testing or medical care. Of the 63 surveyed study participants, 39 (68%) of 57 would prefer self-testing among other testing choices in the future.

Conclusions: Grindr™ users seeking HIV self-testing are willing to request self-test kits online and found self-test kits acceptable, easy to use, and preferred US mail test delivery. The use of self-test kits identified at least two new cases of HIV infection among respondents; both sought medical care. HIV self-testing promotion through social networking applications has a high potential to reach untested high-risk populations who will link to care if positive.

1099 Sexually Transmitted Disease Partner Services Increase HIV Testing Among Men Who Have Sex With Men

Matthew R. Golden[1]; David A. Katz[1]; David Kern[2]; David Heal[2]; Roxanne Kerani[1]; Julia C. Dombrowski[1]

[1]University of Washington, Seattle, WA, US; [2]Washington State Department of Health, Tumwater, WA, US

Background: MSM with bacterial sexually transmitted infections (STI) are at elevated risk for HIV infection. Only approximately half of such men are HIV tested at time of their STI diagnosis or treatment. We instituted and evaluated a program promoting HIV testing through public health STI partner services (PS).

Methods: Starting in May 2012, health departments in WA State, USA, revised PS programs with the objective of providing PS to all MSM with early syphilis, gonorrhea or chlamydial infection, and ensuring that all MSM without a prior HIV diagnosis tested for HIV. PS staff recorded HIV testing as an explicit PS outcome. We compared the percentage of MSM without a prior HIV diagnosis who tested for HIV within four weeks of STD diagnosis or treatment in the period before (March 2010-April 2012) and during the revised program (May 2012-June 2014). New HIV diagnoses were ascertained through HIV surveillance. Negative HIV testing was ascertained through PS and confirmed with medical providers or test records when possible. We used chi-square tests and logistic regression to compare the precentages of MSM receiving PS, HIV testing and newly diagnosed with HIV.

Results: Among MSM without a prior HIV diagnosis, 1896 (62%) of 3083 in the pre-intervention period and 3367 (76%) of 4435 in the intervention period received PS (p<.001). The percentage of MSM receiving PS tested for HIV increased from 63 to 91% concurrent with the intervention (p<.001). PS recipients were more likely to be newly HIV diagnosed then men who did not receive PS in both the pre-intervention (0.93 vs. 2.5%, p=.002) and the intervention periods (1.4 vs. 2.4%, p=.050). The percent of all MSM newly diagnosed with HIV in the state who had a concurrent STI diagnosis increased from 7.7 to 15.2% (p<.001). Among all MSM with bacterial STI (including men who did not receive PS), 59 (1.9%) in the pre-intervention period and 96 (2.2%) in the intervention period were newly diagnosed with HIV infection (p=45). On multivariable analysis, being newly diagnosed with HIV was independently associated with having early syphilis or rectal gonorrhea (p<.001 for both), but not with intervention period.

Conclusions: Promoting HIV testing through STI PS is feasible and increases HIV testing among men at high risk for HIV infection. It is uncertain whether the increase in HIV case-finding among MSM with bacterial STI observed concurrent with our intervention reflects an intervention effect, or a general increase in simultaneous STI and HIV testing among MSM.

1100 Expanding HIV Testing in Hospital Emergency Departments and Inpatient Admissions

Pollyanna R. Chavez[1]; Elizabeth Greene[2]; Kate Buchacz[1]; Theresa Gamble[2]; Steven F. Ethridge[1]; Laura McKinstry[3]; Gheetha Beauchamp[3]; Matthew Connor[3]; Wafaa M. El-Sadr[4]; Bernard M. Branson[1]

[1]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US; [2]FHI360, Durham, NC, US; [3]Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, US; [4]Columbia University, New York, NY, US

Background: The Expanded HIV Testing (EHT) component of HPTN 065, the Test, Link to Care, Plus Treat (TLC-Plus) study, aimed to evaluate if it is feasible to increase HIV testing though universal offering of HIV testing during inpatient (IP) and emergency department (ED) admissions at participating hospitals in the Bronx, NY (NY), and Washington, DC (DC), and shift to laboratory-based (LB) from point-of-care (POC) rapid HIV testing.

Methods: We analyzed testing data from February 1, 2011, to January 31, 2014, for IP admissions and ED visits from 7 participating hospitals in DC and 9 in NY. Indicators for each municipality included testing percentages (the total number of ED visits or IP admissions during which an HIV test was conducted among the total number of ED visits or IP admissions), the percentage of positive tests, and the number of tests conducted by type (POC or LB) for each 12- month period during the study. We assessed trends in testing percentages and positivity percentages across time via Cochran-Armitage chi-square analysis.

Results: Throughout the 3-year study period, the percentages of IP admissions with testing provided increased from 22.67% in year 1 to 24.09% in year 3 in DC (p<0.0001) and from 12.96% to 13.60% in NY (p<0.0001). For IP admissions in NY hospitals, the percentage of LB HIV tests increased from 28.84% to 55.79% (p<0.0001) and the percentage of positive tests increased from 1.45% to 2.26% (p<0.0001). For IP in DC hospitals, the percentage of LB HIV tests decreased from 96.72% to 82.91% (p<0.0001) and the percentage of positive tests also decreased from 4.87% to 3.99% (p<0.001). The percentage of ED visits with testing provided increased from 6.59% to 6.91% (p<0.0001) in NY and increased from 11.20% to 15.87% in DC hospitals (p<0.0001). LB testing in EDs increased from 0.27% to 19.95% in NY and from 5.09% to 26.58% in DC (p<0.0001). DC EDs reported an increase in the percentage of positive tests, from 0.60% to 0.84% (p<0.0001) and in NY EDs the percentage of positive tests remained essentially unchanged.

Table 1. Expanded HIV testing implementation indicators in hospital emergency department visits and inpatient admissions, Washington, DC and Bronx, NY, US, 2011-2013: Data from the TLC-Plus (HPTN 065) Study

	Bronx, NY			Washington DC		
	February 2011 -January 2012	February 2012 -January 2013	February 2013 -January 2014	February 2011 -January 2012	February 2012 -January 2013	February 2013 -January 2014
Inpatient Admissions n	122,021	120,900	118,824	48,668	58,321	57,025
HIV Tests n (%)	15,811 (12.96)	15,112 (12.50)	16,163 (13.60)	11,034 (22.67)	12,496 (21.43)	13,735 (24.09)
POC rapid tests n (%)	11,251 (71.16)	8,937 (59.14)	7,145 (44.21)	362 (3.28)	1,359 (10.88)	2,347 (17.09)
Lab-based tests n (%)	4,560 (28.84)	6,175 (40.86)	9,018 (55.79)	10,672 (96.72)	11,137 (89.12)	11,388 (82.91)
HIV Positive Tests n (%)	230 (1.45)	251 (1.66)	366 (2.26)	537 (4.87)	562 (4.50)	548 (3.99)
ED Visits n	525,137	555,113	540,766	275,301	281,623	249,894
HIV Tests n (%)	34,620 (6.59)	34,166 (6.15)	37,390 (6.91)	30,840 (11.20)	37,855 (13.44)	39,654 (15.87)
POC rapid tests n (%)	34,525 (99.73)	33,522 (98.12)	29,931 (80.05)	29,270 (94.91)	36,165 (95.54)	29,113 (73.42)
Lab-based tests n (%)	95 (0.27)	644 (1.88)	7,459 (19.95)	1,570 (5.09)	1,690 (4.46)	10,541 (26.58)
HIV Positive Tests n (%)	153 (0.44)	122 (0.36)	133 (0.36)	186 (0.60)	175 (0.46)	332 (0.84)

Expanded HIV testing implementation indicators in hospital emergency department visits and inpatient admissions, Washington, DC and Bronx, NY, US, 2011-2013: Data from the TLC-Plus (HPTN 065) Study

Conclusions: During the 3 years of EHT, the percentage of IP admissions and ED visits with an HIV test showed little change. However, use of POC rapid tests diminished as the adoption of lower cost LB testing increased, providing opportunities for more efficient future scale-up of HIV testing.

1101 Universal HIV Testing Using a "Hybrid" Approach in East Africa in the SEARCH Trial

Gabriel Chamie[1]; Tamara Clark[1]; Jane Kabami[3]; Kevin Kadede[2]; Dalsone Kwarisiima[3]; Norton Sang[2]; Maya Petersen[4]; Moses R. Kamya[3]; Diane Havlir[1]; Edwin Charlebois[5]

[1]University of California San Francisco, San Francisco, CA, US; [2]Kenyan Medical Research Institute (KEMRI), Nairobi, Kenya; [3]Makerere University - University of California Research Collaboration, Kampala, Uganda; [4]University of California Berkeley School of Public Health, Berkeley, CA, US; [5]University of California San Francisco (UCSF), San Francisco, CA, US

Background: Rapid scale-up of HIV testing to reach the 2014 UNAIDS testing target of 90% coverage in sub-Saharan Africa will likely require concurrent implementation of multiple mobile testing approaches. We sought to test the effectiveness of a "hybrid" mobile HIV testing approach of multi-disease community health campaigns followed by home-based testing (HBT), to achieve population-wide coverage.

Methods: From 2013-2014, we enumerated 168,336 adult (≥15 years) residents of 32 communities in eastern (N=10) and southwestern (N=10) Uganda, and western Kenya (N=12) using a 2-4 week door-to-door census as part of a cluster-randomized HIV test and treat trial (SEARCH: NCT01864603). "Stable" residence was defined as living in a community for ≥6 months over the past year. In each community we performed a 2-week mobile, multi-disease community health campaign (CHC) that included HIV testing, counseling (HTC) and linkage to care; CHC non-participants were then approached for HBT over an average of 1-2 months. We measured population HIV testing coverage and determined characteristics associated with CHC vs. home testing, and associated with no testing, using multivariable logistic regression and accounting for clustering by household.

Results: HIV testing was achieved in 89% (130,051) of stable adult residents (N=146,513), and 80% (134,697) of all adults. Adult HIV prevalence was 9.4%, with a median adult CD4+ count of 516 (IQR: 356-705) cells/μL. Of adults tested, 43% reported no prior HIV testing. Among CHC attendees, 99% accepted HIV testing. Overall, 103,503 stable adult residents tested via CHCs (80%), and 26,548 tested via HBT (20%). CHC-based HTC uptake varied by community, ranging from 60-93% of stable adults tested. In multivariate analyses of stable adults who tested, predictors of not attending the CHC (i.e., needing HBT) were: male gender, single marital status, HIV infection, non-farming occupation, higher education status, study region, and more time away from community in the year prior to study initiation (Table: Model 1). Predictors of failure to HIV test at either CHC or HBT were similar to those associated with CHC non-participation (Table: Model 2).

Table. Logistic regression models predicting testing effectiveness, controlling for age and variables in table.

	Model 1: Predictors of not testing via CHC (aOR (95% CI))	Model 2: Predictors of not testing (aOR (95% CI))
Male sex (vs. female)	1.64 (1.59-1.70)	1.66 (1.61-1.73)
Single (vs. married)	1.34 (1.28-1.41)	1.20 (1.14-1.27)
HIV-infected (vs. uninfected)	1.10 (1.04-1.15)	N/A
Any secondary education (vs. none)	1.19 (1.12-1.26)	1.30 (1.21-1.39)
Non-farmer (vs. farmer)	1.52 (1.47-1.58)	1.42 (1.36-1.48)
Southwestern Uganda (vs. eastern Uganda) Western Kenya (vs. eastern Uganda)	1.27 (1.21-1.33) 2.35 (2.25-2.45)	1.15 (1.10-1.21) 1.44 (1.37-1.51)
Months away from community in year prior to enrollment (up to 6 months)	1.21 (1.19-1.23) per each additional month away	1.21 (1.20-1.23) per each additional month away

Conclusions: We achieved rapid, near-universal HTC coverage (89%) of 146,513 stable adult residents across 32 communities in Uganda and Kenya using a hybrid, mobile approach of multi-disease community health campaigns and home-based testing. Despite high HIV testing coverage, men and mobile populations remain challenges for universal testing.

1102 A Household Food Voucher Increases Consent to Home-Based HIV Testing in Rural KwaZulu-Natal

Mark McGovern[1]; David Canning[1]; Frank Tanser[2]; Kobus Herbst[2]; Dickman Gareta[2]; Tinofa Mutevedzi[2]; Deenan Pillay[2]; Till Barnighausen[1]

[1]Harvard University, Cambridge, MA, US; [2]Wellcome Trust Africa Centre for Health and Population Studies, University of KwaZulu-Natal, KwaZulu-Natal, South Africa

Background: Despite the importance of HIV testing for controlling the HIV epidemic, testing rates remain low in many countries. Growing emphasis on HIV treatment-as-prevention will require increases in the frequency and coverage of testing to place individuals on treatment rapidly after diagnosis, and new waves of testing will need to reach populations who have not previously tested. Home based testing is one potentially promising approach for supporting this goal. However, testing rates during home visits can be low, particularly in settings with high HIV prevalence, and there is little existing evidence on the effectiveness of interventions to increase testing rates for home based visits. This study tests the hypothesis that unconditional gift vouchers can be used to increase consent rates for home-based HIV testing.

Methods: This study uses data on 18,478 men and women who participated in the 2009 and 2010 Africa Center HIV surveillance cohorts in rural KwaZulu-Natal, South Africa. In 2010, HIV prevalence was 24%, and 41% consented to test for HIV. All residents aged 15 and older are eligible for the HIV surveillance. A subset of households in the 2010 cohort were provided with a gift in the form of a food voucher worth 50 South African Rand (5 USD) which was not conditional on consenting to test. We compare the change in HIV test consent rates between 2009 and 2010 for residents in households that received a voucher in 2010, with the change in HIV test consent rates for residents in households that did not receive a voucher in 2010. Our approach corrects for unobserved confounding using a quasi-experimental difference-in-differences design.

Results: Allocation of the voucher to a household in 2010 increased the probability of household members consenting to test in 2010 by 29 percentage points (risk difference 95% CI 23 - 35; p<.001). We also find an attenuated effect of treatment on consent rates in 2011. Rates of consent to test by intervention group (being a member of a household which received the voucher in 2010) are shown in figure 1. We estimate the cost of the program at 7 USD per additional HIV test obtained.

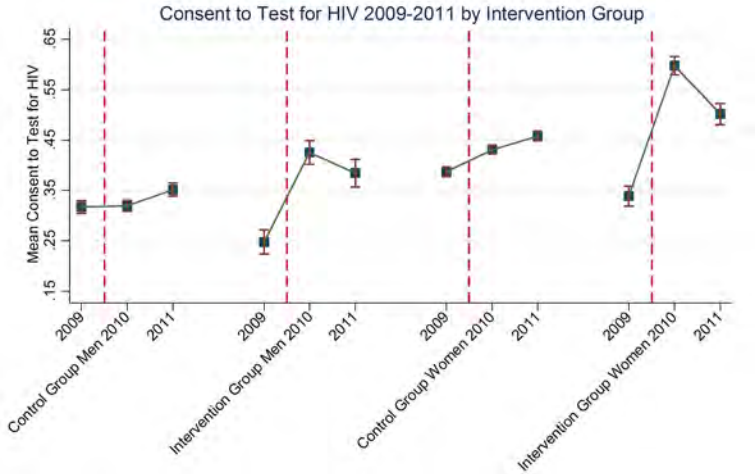


Figure 1: The intervention group is defined as being a member of a household which received the gift voucher in 2010, while the control group is defined as being a member of a household which did not receive the voucher in 2010. Mean consent to test is the number of residents in each group who consented to take a HIV test, divided by the number of residents who were eligible for participation and were successfully contacted by the surveillance surveyors in each group.

Conclusions: The provision of gift vouchers to surveillance participants is likely to be a cost-effective tool for raising consent rates for home-based HIV testing. In addition, by persuading respondents who would ordinarily refuse to test in the absence of the voucher effect, this approach can potentially be used to assess the extent of selection bias in the population.

1103 Acceptability and Uptake of Home-Based HIV Self-Testing in Lesotho

Allison V. Zerbe[1]; Abby L. DiCarlo[1]; Joanne E. Mantell[2]; Robert H. Remien[2]; Danielle D. Morris[1]; Koen Frederix[1]; Blanche Pitt[1]; Zachary J. Peters[1]; Wafaa M. El-Sadr[1]
[1]ICAP at Columbia University, New York, NY, US; [2]HIV Center for Clinical and Behavioral Studies, New York State Psychiatric Institute & Columbia University, New York, NY, US

Background: With 61% of men and 31% of women aged 15-49 never tested as of 2009, HIV testing is a priority in Lesotho. HIV self-testing is one potential strategy to address low testing rates and achieve universal testing coverage, by complementing voluntary and provider-initiated testing. However, little is known about the acceptability of self-testing in Lesotho. This feasibility study explored the acceptability and uptake of home-based self-testing (HBST) in a sample of Basotho women and men.

Methods: Between December 2013 and May 2014, 45 HIV-positive index participants (IPs) were recruited from 4 health centers in Mafeteng and Mohale's Hoek in Lesotho as part of the NIH-funded Enhanced Prevention in Couples (EPIC) study. Home visits were scheduled with IPs to offer HIV testing to their household (HH) members. HH members were offered two options for testing: (1) standard HIV counseling and testing (SCT); or (2) HBST with OraQuick ADVANCE HIV-1/2, followed by confirmatory standard HIV testing. Demographic and acceptability measures were collected through in-person surveys.

Results: Seventy-three percent of IPs were recruited from antenatal and 24% from TB clinics; 84% of IPs were women. A total of 88 HH members were offered testing, and 59 (67%) accepted; 78% of men and 61% of women agreed to test. Almost all (98%) participants chose the HBST option. All HBST participants described the self-testing process as "easy" or "very easy"; 12% required extra instruction. Participants were asked to identify positive and negative aspects of HBST. Ninety-eight percent of participants reported only positive qualities, including the home visit itself (32%); the openness and respectfulness of the study team (25%); the pain-free testing method without need for a prick or blood-draw (25%); the ability to test oneself (19%); being the first to know one's status (14%); the simplicity of the testing procedure (14%); the privacy and confidentiality of testing at home (7%); having an option for testing (standard or self) (7%); and the rapidity of the test (7%). Nearly all participants reported that they would recommend HBST to friends and family. Thirteen percent of participants were newly diagnosed as HIV-positive.

Conclusions: This study demonstrates high levels of uptake and acceptability for HBST and the feasibility of utilizing HIV-positive index individuals as a way to reach others in their households, who may not access health facilities. Successfully reaching men is an added advantage.

TUESDAY, FEBRUARY 24, 2015

Session P-Z1 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Costs and Cost Effectiveness

1104 The Lifetime Medical Cost Savings From Preventing HIV in the United States

Bruce R. Schackman[1]; John Fleishman[6]; Amanda Su[2]; Richard Moore[5]; Rochelle Walensky[2]; David Paltiel[3]; Milton Weinstein[4]; Kenneth Freedberg[2]; Kelly Gebo[5]; Elena Losina[2]
[1]Weill Cornell Medical College, New York, NY, US; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, US; [3]Yale School of Public Health, New Haven, CT, US; [4]Harvard School of Public Health, Boston, MA, US; [5]Johns Hopkins University School of Medicine, Baltimore, MD, US; [6]Agency for Healthcare Research and Quality, Rockville, MD, US

Background: Enhanced HIV prevention interventions, such as pre-exposure prophylaxis for high-risk individuals, require substantial investments. We sought to estimate the medical cost saved by averting one HIV infection in the United States.

Methods: We estimated lifetime medical costs in persons with and without HIV to determine the cost saved by preventing one HIV infection. We used a computer simulation model of HIV disease and treatment (CEPAC) to project CD4 cell count, antiretroviral treatment status, and mortality after HIV infection. Annual medical cost estimates for HIV-infected persons, adjusted for age, sex, race/ethnicity, and transmission risk group, were from the HIV Research Network (range $1,854-$4,545/month) and for HIV-uninfected persons were from the Medical Expenditure Panel Survey (range $73-$628/month). Results are reported as lifetime medical costs from the US health system perspective discounted at 3% (2012 US dollars).

Results: The estimated discounted lifetime cost for persons who become HIV infected at age 35 is $326,500 (60% for antiretroviral medications, 15% for other medications, 25% for non-drug costs). For individuals who remain uninfected, but at high risk for infection, the discounted lifetime cost estimate is $96,700. The medical cost saved by avoiding one HIV infection is $229,800. The cost saved would reach $338,400 if all HIV-infected individuals presented early and remained in care. Cost savings are higher taking into account secondary infections avoided and lower if HIV infections are temporarily delayed rather than permanently avoided.

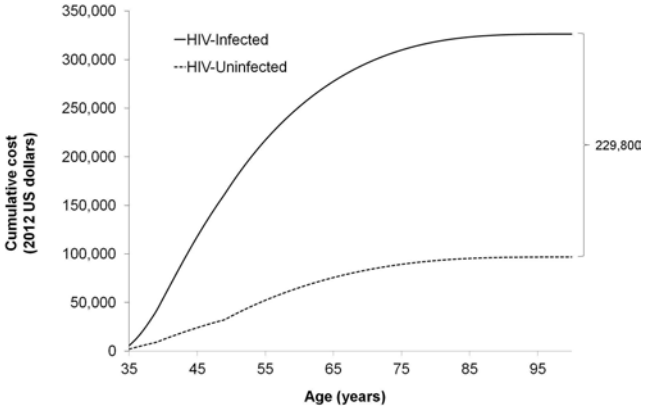


Figure 1: Cumulative discounted lifetime costs from time of infection at age 35 (2012 US dollars)

Conclusions: The potential medical cost savings from HIV prevention in the US are substantial given the high cost of HIV disease treatment.

1105 Online Partner Notification: A Cost-Effective Tool to Reduce HIV-1 Epidemic Among MSM

Brooke E. Nichols[1]; Hannelore M. Götz[2]; Eric C. van Gorp[1]; Annelies Verbon[3]; Casper Rokx[3]; Charles Boucher[1]; David A. van de Vijver[1]

[1]Erasmus University Medical Center, Rotterdam, Netherlands; [2]Public Health Service Rotterdam-Rijnmond, Rotterdam, Netherlands; [3]Erasmus Medical Center, Rotterdam, Netherlands

Background: Earlier antiretroviral treatment initiation prevents new HIV infections. Unfortunately, a key problem in HIV prevention and care is the high number of patients diagnosed late as these undiagnosed patients can continue forward HIV-1 transmission. Partner notification is a tool that can identify HIV infected patients earlier. These patients can then start treatment sooner which can then reduce the number of infections to others. The aim of this study is to use mathematical modeling to determine the preventative impact and cost-effectiveness of partner notification on new HIV-1 infections. For this purpose, we used data from the Rotterdam-Rijnmond Public Health Service (the Netherlands) which has implemented an online partner notification system that has successfully identified persons at risk of infection by using an anonymous notification system via the contacts of recently diagnosed patients.

Methods: A model was validated and accurately reconstructed the Dutch HIV epidemic among MSM from 2008 through 2012. Late diagnoses are common among MSM in the Netherlands: 37% had CD4 <350 cells/μl including 20% with CD4 <200 cells/μl. The online partner notification system resulted in nine new HIV diagnoses among 366 MSM notified for any STI and tested for HIV in 2013. This represented 3% of all new diagnoses in the region. Costs and quality adjusted life years (QALYs) were assigned to each disease state and calculated over a 5, 10 and 20 year period. Cost-effectiveness ratios were obtained for the use of partner notification to identify 3% of all new diagnoses versus no partner notification.

Results: Partner notification is predicted to avert a total of 14 infections (interquartile range [IQR] 10-18) over the course of 5 years countrywide to 148 (IQR 98-205) over 20 years. Partner notification was considered borderline cost-effective in the short term, with increasing cost-effectivity over time: €54,035 (IQR €52,578-€54,655), €21,307 (€20,411-€21,984) and €8,619 (€7,864-€9,541) per QALY gained over a 5, 10, and 20 year period, respectively. The full monetary benefits of partner notification by preventing new HIV infections become more apparent over time.

Conclusions: The partner notification tool is a cost-effective tool for HIV prevention in MSM in the long run, with little additional effort required from healthcare professionals. There is also an additional clinical benefit of both early identification of HIV and identification and treatment of other STIs.

1106 Cost-Effectiveness of Preexposure Prophylaxis for High-Risk HIV-Discordant Couples

Roger Ying[1]; Renee Heffron[1]; Jared Baeten[1]; Connie Celum[1]; Elly Katabira[2]; Nulu Bulya[2]; Ruanne V. Barnabas[1]

[1]University of Washington, Bellevue, WA, US; [2]Makerere University College of Health Sciences, Kampala, Uganda

Background: Antiretroviral-based HIV prevention strategies, including antiretroviral treatment (ART) for HIV-positive persons and pre-exposure prophylaxis (PrEP) for HIV-negative persons, have the potential to reduce HIV transmission, but questions remain regarding the cost of implementation.

Methods: We estimated the incremental costs of screening and providing high-risk HIV discordant couples with ART for the HIV-positive partner and six months of PrEP for the HIV-negative partner, based on the design of an ongoing PrEP and ART demonstration project in Kampala, Uganda. Micro-costing and time and motion studies were conducted in February 2014. The cost analysis was conducted from the programmatic perspective over a 10-year time horizon and includes all incremental clinical costs incurred and averted. We used a mathematical model parameterized for HIV transmission in Uganda to compare the incremental cost-effectiveness ratio (ICER) of the high-risk discordant couples ART and PrEP program to increasing ART coverage to 70% of HIV-positive persons with CD4≤500 cells/μL. In the model, high-risk discordant couples were defined as couples with projected annual HIV incidence of >6%.

Results: Based on enrollment and retention rates in the demonstration project, 73% of screened couples would be enrolled and 97% of couples would be retained in care at one year. Using current Ministry of Health costs, the annual incremental cost per couple is $454, with the majority of costs attributable to laboratory monitoring (54%). With public-sector salaries and annual PrEP drug costs reduced to $75 per person, the annual incremental cost per couple is $322. Use of point-of-care viral load tests and task shifting with brief directed counseling further reduces the annual incremental cost per couple to $92, with laboratory monitoring decreasing to 37% of the cost. The ICER of PrEP and ART for high-risk discordant couples was $1,001 per HIV infection averted at 10 years. Scaling up ART for persons with CD4≤500 cells/μL without PrEP was less cost-effective. However, an ART program for persons with CD4≤500 cells/μL is more cost-effective for increasing quality-adjusted life-years (QALYs) at $245 per QALY gained versus $1,146 per QALY gained in the PrEP program.

Table 1. Incremental Cost-Effectiveness Ratios (ICER) of ART and PrEP strategies for southwest Uganda. Results are shown for a 10-year time horizon relative to 2014. All costs are discounted by 3% annually.

Outcome	Scenario	Effectiveness	Cost (millions USD)	ICER
HIV Infections Averted	**Baseline: Current ART uptake** **ART:** Baseline (40%)* **PrEP:** N/A	Baseline	Baseline	Baseline
	ART scale up only (no PrEP) **ART:** CD4≤500 cells/μL (70%) **PrEP:** N/A	11,983	14·0	Dominated†
	MoH adds ART and PrEP for SDCs without VL screening **ART:** Baseline (40%)* + high-risk SDC‡ without CD4/VL criteria (80%) **PrEP:** High-risk SDC‡ (80%)	26,063	26·1	$1,001
QALYs Gained	**Baseline: Current ART uptake** **ART:** Baseline (40%)* **PrEP:** N/A	Baseline	Baseline	Baseline
	ART scale up only (no PrEP) **ART:** CD4≤500 cells/μL (70%) **PrEP:** N/A	57,070	14·0	$245
	MoH adds ART and PrEP for SDCs without VL screening **ART:** Baseline (40%)* + high-risk SDC‡ without CD4/VL criteria (80%) **PrEP:** High-risk SDC‡ (80%)	67,639	26·1	$1,146

*Under current guidelines
†A dominated strategy is less cost-effective than a combination of other strategies.
‡High-risk discordant couples are those in which the projected HIV incidence is >6%.

Conclusions: Using PrEP as a bridging strategy in discordant couples until the HIV-positive partner is on ART for 6 months may cost-effectively combine the preventive benefit of PrEP with the therapeutic benefit of ART until the HIV-positive partner is virally suppressed.

1107 Multipurpose Prevention Technologies for HIV and Pregnancy Prevention

Rebecca Geary; **Jennifer Smith**; Nidhi Khurana; Ide Cremin; Timothy Hallett
Imperial College London, London, United Kingdom

Background: Multipurpose prevention technologies (MPTs) to prevent both HIV and unintended pregnancy could create important opportunities in terms of cost efficiencies, higher acceptability (compared to HIV-prevention only products) and a reduced adherence burden for users. Women with unmet need for dual protection against unintended pregnancy and HIV infection are a priority for prevention interventions. MPTs could add to the limited number of much-needed female-controlled HIV prevention methods and increase contraceptive method choice. Their potential impact and cost-effectiveness has not been fully analysed.

Methods: We modeled the introduction of an MPT vaginal ring in South Africa and examined HIV and reproductive health outcomes. We assumed a range of efficacy estimates for HIV prevention (60-80%) and pregnancy (92-97%), and different delivery strategies (horizontal and vertical, prioritising up to 10% of different age and risk groups). We examined the health impact and estimated the cost-effectiveness for the introduction of the MPT relative to existing prevention measures per HIV incident infection and disability adjusted life year (DALY) averted.

Results: The MPT could avert 1.6-2.9% of new HIV infections among women aged 15-49 years, 4.3-4.6% of maternal deaths and 1.5-1.6% of DALYS among women aged 15-49 years that would occur between 2018 and 2025 using a delivery strategy that targets 10% of 15-29 year-olds and 5% of 30-49 year-olds. The majority of DALYS averted are derived from reproductive health outcomes, primarily due to the reduction in maternal deaths. The influence of the chosen delivery strategy outweighs variations in product efficacy in terms of the MPT impact on health. A multipurpose intra-vaginal ring could be very cost-effective ($200 to $2,700 per DALY averted) when delivered through either horizontal or vertical programmes.

Conclusions: The use of MPTs could substantially and cost-effectively generate health among women in South Africa. However the success of MPTs, with regard to both impact and cost effectiveness, will be determined by the delivery strategy of a product rather than its efficacy and cost. We urge for operational studies to be conducted to evaluate the feasibility of potential delivery strategies of MPTs for women. New and forthcoming data on the MPT delivery costs and women's preferences will be critical for determining their use across different settings.

1108 Cost-Effectiveness of Isoniazid Preventative Therapy for HIV-Infected Pregnant Women in India

Sunaina Kapoor; Natasha Chida; Amita Gupta; **Maunank Shah**
Johns Hopkins University School of Medicine, Baltimore, MD, US

Background: Pregnancy increases the risk of active Tuberculosis (TB) infection particularly in HIV-infected women. Co-infection can result in increased morbidity and mortality for both mother and child. Isoniazid preventative therapy (IPT) may reduce progression to active TB in HIV-infected individuals, but confers risks of drug toxicity in pregnant women and added costs. Globally, India has both the highest number of incident TB cases and a high burden of HIV. The epidemiology of this co-infection in India differs substantially from that of other high HIV and TB burden countries like South Africa. The cost-effectiveness of IPT for HIV-infected pregnant women in India is unknown.

Methods: An economic evaluation from the health-system perspective was performed using a decision analytic model to determine the cost-effectiveness of antepartum IPT among HIV-infected pregnant women (all assumed to be on anti-retroviral therapy) in India. We compared two antepartum TB preventative strategies with the current practices in India (no IPT): Intervention 1 (6 months IPT for all HIV-infected women regardless of CD4 cell count) and Intervention 2 (6 months IPT for HIV-infected pregnant women with CD4 cell counts ≤ 200 cells/μl). Primary outcomes were anticipated costs, disability-adjusted life years (DALYs), active TB cases, and TB related deaths. Cost-effectiveness was represented using incremental cost-effectiveness ratios (ICERs).

Results: Both interventions (1) IPT for all HIV-infected pregnant women and (2) IPT only for those women with CD4 cell counts ≤ 200 cells/μl were found to improve health outcomes compared to no IPT. Intervention 1 resulted in the greatest improvement in health outcomes with 21 active TB cases averted per 1000 patients and 10 active TB deaths averted per 1000 patients at an incremental cost of $20.26 per individual. Intervention 2 also showed improved health outcomes with 3 active TB cases averted per 1000 patients

and 2 active TB deaths averted per 1000 patients at an incremental cost of $2.01 per individual. Both Intervention 1 and Intervention 2 were found to be highly cost effective compared to no IPT with associated ICERs of $115.77 and $100.50/DALYs-averted respectively, at a willingness-to-pay threshold of Indian per capita GDP ($1500/DALYs-averted).

Table 1. Costs and Effects of 6 Month IPT Interventions Compared to No IPT in Base Case

Variable	Intervention 1: Treat All (95% UR)	Intervention 2: Treat CD4 cell counts ≤ 200 cells/μl (95% UR)	No IPT (95% UR)
Costs ($ USD)			
Net Costs (*per individual*)	$22.53 ($14.31-$72.69)	$4.28 ($3.83-$36.94)	$2.27 ($1.09-$11.43)
Incremental	$20.26 ($9.50-$69.39)	$2.01 ($0.91-$30.98)	$0
Effects			
DALYs (*per individual*)	14.639 (6.544-22.184)	14.794 (6.803-22.358)	14.814 (6.831-22.405)
Incremental	0.175 (0.068-1.511)	0.032 (0.013-0.868)	0
Deaths (deaths per 1000 pts)*	11 (7-72)	19 (11-98)	21 (12-128)
Incremental	10 (5-83)	2 (1-42)	0
Active TB (cases per 1000 pts)	16 (1-99)	34 (16-143)	37 (19-176)
Incremental	21 (15-130)	3 (2-61)	0
Cost-Effectiveness (ICERs)			
Base-Case ($/DALY averted)	115.77 (12.63-608.91)	100.50 (10.34-648.345)	0

*Deaths due to Active TB Infection or IPT-related Hepatotoxicity

Conclusions: Implementation of 6 months of antepartum IPT for HIV-infected women (with or without CD4 cell count stratification) is a highly cost-effective strategy for prevention of TB compared to current practices in India.

1109 Epidemiologic Benefits and Cost-Effectiveness of Improving Rwanda's HIV Care Cascade

Eran Bendavid[1]; Edward Mills[2]; Steve Kanters[2]; Sabin Nsanzimana[3]

[1]Stanford University, Stanford, CA, US; [2]University of Ottawa, Ottawa, Canada; [3]Rwanda Biomedical Center, Kigali, Rwanda

Background: Connecting HIV+ individuals to treatment programs and sustaining effective antiretroviral therapy (ART) is a challenge in developing countries. The implications of addressing patient linkage and retention are not only partially characterized. We use the national coverage of data on HIV care in Rwanda to estimate the epidemiologic benefits and cost-effectiveness of improving the HIV care cascade.

Methods: We parameterized an HIV disease and transmission simulation model to reflect the epidemic in Rwanda using age-structured prevalence and detailed information on ART program. The care cascade was modeled as a time-dependent process of patient loss between diagnosis and initial staging, staging and ART initiation, and loss after ART initiation. Costs were obtained from a top-down accounting of HIV testing, treatment, and laboratory monitoring in Rwanda. Alternative scenarios included improving HIV testing to 100% of the population, perfect linkage from testing to staging, and reduction of pre-ART and post-ART patient leakage to 0%. In addition, we simulated a strategy of immediate treatment among patients linked to care, as opposed to treatment initiation at CD4<350 cells/mm^3. Model and parameter uncertainty were estimated using Monte Carlo and probabilistic simulations.

Results: We calibrated the model to Rwanda's adult HIV prevalence between 2004 and 2013, a drop from 3.6% to 2.8%. Incidence reduction was greatest under a scenario of combined perfect system performance, including immediate ART initiation (49% reduction in 10 years (uncertainty bounds 39-60%)), followed by immediate treatment initiation (36%, 28-43%) and reduction of post-ART patient loss (14%, 5-22%). Using a unit-cost approach to estimate the total costs of scaling up HIV treatment and services, we estimate that adopting immediate ART initiation will cost approximately $120 million additional to the status quo (discounted at 3% annually). The incremental cost-effectiveness of immediate ART initiation was estimated at $1,094 per life-year gained (556-1922), and that of a perfect system performance, including immediate ART initiation was $1,803 (1122-2912) per life-year gained. No other scenario was cost-effective.

Conclusions: Using national data on ART care and treatment in Rwanda, we demonstrate that the greatest epidemiologic benefits are likely to result from immediate ART initiation. While the budgetary implications of immediate initiation are large, this approach is cost-effective in Rwanda by traditional standards.

1110 The Cost-Effectiveness of Early ART Initiation in South Africa: A Quasi-Experiment

Jacob Bor[1]; Ellen Moscoe[2]; Natsayi Chimbindi[3]; Kobus Herbst[3]; Kevindra K. Naidu[3]; Frank Tanser[3]; Deenan Pillay[3]; Till Barnighausen[3]

[1]Boston University School of Public Health, Boston, MA, US; [2]Harvard School of Public Health, Boston, MA, US; [3]Wellcome Trust Africa Centre for Health and Population Studies, Somkhele, South Africa

Background: Clinical trials are not well suited to evaluate the effectiveness and cost-effectiveness of interventions in "real world" settings. Using a quasi-experimental regression-discontinuity design (Bor et al. 2014), we establish the causal effect of early (vs. deferred) ART initiation on patient survival in rural South Africa, and obtain empirical (as opposed to modeled) cost-effectiveness estimates.

Methods: Demographic data from a large population surveillance in rural KwaZulu-Natal were linked to clinical records from South Africa's public sector ART program. 4391 patients enrolled in HIV care between 2007 and 2011. CD4 counts were collected upon entry into care regardless of ART initiation. Subjects were eligible for ART if CD4 < 200 cells/μL, as per national guidelines during this period. Dates of death were obtained from the demographic surveillance; dates of initiation and follow-up CD4 counts were obtained from clinical records. Patients were followed for up to five years. We estimated the causal effect of immediate ART eligibility on survival, immune health, and time spent in pre-ART and on ART, which were used to estimate costs. Effects were estimated using a regression-discontinuity design, which exploits the quasi-random nature of treatment assignment for patients with first CD4 counts close to the eligibility threshold. Patients just above vs. just below the threshold are similar on all observed *and unobserved* factors; but they receive different treatment assignments.

Results: Patients presenting with a CD4+ count just below 200 cells/μL were 4.3% points (95% CI 0.6, 8.0) more likely to be alive at two years compared to patients presenting with a CD4+ count just above the cut-off, an advantage that persisted at five years (Fig 1). These effects imply a 14.9% point two-year survival advantage for patients who actually initiated ART because they had an eligible CD4+ count. Large, persistent gains in clinical immune function were also observed among patients who were ART eligible. Over a five-year horizon, the additional medical care provided to ART-eligible patients implied a cost of $1967 per life year saved compared to treating patients with CD4+ counts close to 200 cells/μL.

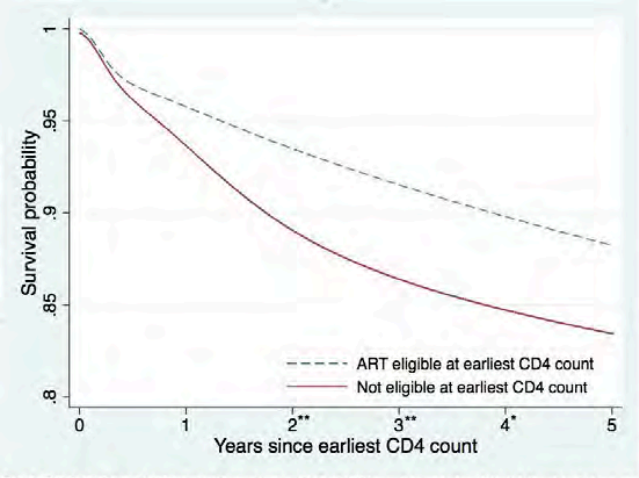


Fig 1. Predicted survival curves for patients with first CD4 counts just below (eligible) and just above (not eligible) the 200-cell threshold. Survival curves were estimated based on flexible-parametric survival models, adapted for use in regression discontinuity designs.

Reference: Bor J, Moscoe E, Mutevedzi P, Newell ML, Bärnighausen T. Regression discontinuity designs in epidemiology: causal inference without randomized trials. Epidemiology. 2014 Sep; 25(5):729-37.

Conclusions: In a real-world setting, referral of patients to pre-ART care (vs. immediate ART eligibility) led to large losses of life and health. These losses could have been avoided with immediate ART, which was found to be "very cost effective" at conventional benchmarks.

1111 Community-Based Strategies to Strengthen the Continuum of HIV Care Are Cost-Effective

Jennifer A. Smith[1]; Monisha Sharma[2]; Carol Levin[2]; Jared Baeten[2]; Heidi van Rooyen[3]; Connie Celum[2]; Timothy Hallett[1]; Ruanne V. Barnabas[2]

[1]Imperial College London, London, United Kingdom; [2]University of Washington, Seattle, WA, US; [3]Human Sciences Research Council, Sweetwaters, South Africa

Background: Closing gaps in the continuum of HIV care is a priority for public health strategies that aim to reduce HIV-associated morbidity, mortality and HIV incidence. Facility-based HIV counselling and testing (HTC) has achieved limited testing coverage and linkage to care, particularly among asymptomatic persons. Home HTC and linkage to care achieved high testing coverage and linkage to care in KwaZulu-Natal, South Africa, but its impact on population-level health and cost-effectiveness compared to existing facility-based testing has not been evaluated.

Methods: We developed an individual-based HIV transmission model parameterized with epidemiologic and cost data from home HTC and linkage studies in rural KwaZulu-Natal, South Africa. The HTC and linkage studies measured the change in the proportion of all HIV-positive persons with suppressed viral load between study enrolment and 12 months. The model simulated the intervention impact and projected the effect on health outcomes over 10 years. The incremental cost-effectiveness ratios (ICERs) were calculated for the intervention relative to existing facility-based testing per HIV incident infection and disability adjusted life year (DALY) averted.

Results: With the high coverage (91%) and linkage to ART (80%) observed in the home HTC studies, HIV-associated disability and incident infections were reduced compared to current testing modalities, especially at higher ART initiation criteria: as the ART initiation threshold increased from ≤200 cells/mm^3 to universal eligibility, 10-22% of DALYs and 11-48% of HIV infections were averted over ten years. Home HTC is "very cost effective" by WHO standards across all ART initiation thresholds: US$1,080, $925, $985 and $1,150 per DALY averted and $7,000, $7,580, $7,100 and $6,560 per infection averted with ART initiation at ≤200 cells/mm^3, ≤350 cells/mm^3, ≤500 cells/mm^3 and universal eligibility, respectively. ART costs exceeded all other costs, accounting for 48-85% of total programme costs; with universal eligibility and a reduced ART cost, the ICER per DALY averted is reduced four-fold.

Conclusions: Home HTC can strengthen linkage to care and enhance the increases in ART uptake that will result from South Africa's expanding ART eligibility criteria. As treatment programs move forward to implement '90% of HIV-infected persons tested, 90% treated, 90% achieving viral load suppression', insights from this analysis find that community-based HTC and linkage is a cost-effective strategy for HIV prevention.

1112 The Cost-Effectiveness of CD4 Cell Count Versus HIV RNA Viral Load for ART Initiation

Roger Ying[1]; Brian Williams[3]; Ruanne V. Barnabas[1]; Reuben Granich[2]

[1]University of Washington, Bellevue, WA, US; [2]Joint United Nations Programme on HIV/AIDS, Geneva, Switzerland; [3]Stellenbosch University, Stellenbosch, South Africa

Background: The UNAIDS has proposed achieving 90% diagnosis of HIV-positive persons, 90% antiretroviral therapy (ART) coverage among those diagnosed, and 90% viral suppression among those on ART. ART initiation guidelines have primarily depended on CD4 cell count, with the World Health Organization (WHO) currently recommending ART initiation for persons with CD4≤500 cells/μL. However, HIV transmission, morbidity, and mortality are more closely linked with the level of virus—viral load (VL)—than CD4 count. The impact of CD4- versus VL-based ART criteria on HIV-associated outcomes has not previously been studied.

Methods: We reviewed the literature for studies assessing the association between clinical outcomes—HIV transmission, time to AIDS, HIV-associated mortality, and ART initiation—and CD4 count and VL. These measures were used to parameterize a compartmental mathematical model of HIV transmission in KwaZulu-Natal, South Africa, that was stratified by gender, CD4 count, VL, and ART status. The model was used to estimate the proportion of ART-ineligible persons with high viral load, and the proportion of HIV infections, deaths, and quality-adjusted life-years (QALYs) that could have been saved if ART had been initiated for those with high VL. These values were estimated from 2004 to 2014 and from 2015 to 2025. From 2015 to 2025, we also estimated the incremental cost-effectiveness ratio (ICER) of ART initiation at VL>10,000 copies/mL to CD4≤500 cells/μL.

Results: We estimate that in KwaZulu-Natal from 2004 to 2014, 35% of ART-ineligible patients by CD4 count had VL >10,000 copies/mL, and 12% had VL>50,000 copies/mL. With 30% of ART-ineligible persons with VL>10,000 copies/mL initiating ART, an additional 72% of HIV infections and 46% of HIV-associated deaths could have been averted, and 44% of QALYs gained. From 2015 to 2025, ART initiation at CD4≤500 cells/μL provides 5% more individuals with ART than VL>10,000 copies/mL. Using the VL criterion results in an ICER of $5,709 per HIV infection averted and $537 per QALY gained, whereas using the CD4 criterion results in an ICER of $7,851 per HIV infection averted and $612 per QALY gained.

Conclusions: By focusing on CD4 measurements rather than HIV viral load, past ART policies missed opportunities to fully utilize the benefits of ART to improve quality-of-life and prevent HIV transmissions. Future HIV prevention strategies should consider focusing on viral load rather than CD4 criteria in order to cost-effectively maximize public health impact.

1113 Costs of Expanded HIV Testing in 4 EDs: Results From HPTN 065

Bruce R. Schackman[1]; Ashley A. Eggman[1]; Jared A. Leff[1]; Megan Braunlin[1]; Bernard M. Branson[2]

[1]Weill Cornell Medical College, New York, NY, US; [2]US Centers for Disease Control and Prevention (CDC), Atlanta, GA, US

Background: HPTN 065 sought to expand HIV testing of emergency department (ED) patients in Bronx, NY and Washington DC between 2011 and 2013. EDs expanded laboratory HIV testing using different processes, resulting in differences in testing costs.

Methods: We conducted micro-costing studies of rapid-result laboratory HIV testing at 2 participating EDs in each jurisdiction in 2013 and compared results to hypothetical costs of an optimized implementation process. Laboratory HIV testing was conducted for ED patients requiring a blood draw for clinical reasons. Costs were estimated by directly observing and interviewing ED directors and staff to document process flows, time estimates, and labor and materials costs. We used national wage and fringe rates and local materials costs to determine the average cost (excluding overhead) per completed non-reactive and reactive HIV test in 2013 US dollars. The optimized process cost was calculated using 4th generation laboratory HIV tests, Multispot confirmatory testing, and a) minimum time estimates for each process flow step, or b) minimum time estimates and lowest wage and materials costs.

Results: Labor time estimates ranged from 7-25 minutes for non-reactive tests and laboratory test volume ranged from 410-500 tests per month. Estimated costs ranged from $17-$24 per completed non-reactive test and $89-$110 per completed reactive test (including confirmatory testing and initial linkage to HIV care activities). Optimized process flow costs were approximately 45% lower for non-reactive tests, primarily due to automating screening eligibility confirmation and ordering of HIV tests, and approximately 20% lower for reactive tests, primarily due to shortening of the time for delivering and documenting test results prior to linking the patient to care (see Table).

Laboratory HIV Testing Costs for ED Patients (2013 US dollars)

		Observed Range Across 4 EDs†	Optimized Process	Optimized Process Using Lowest Wage + Materials Costs
Labor				
	Provide HIV testing information††	0.00-0.82	0.00	0.00
	Confirm HIV screening eligibility	0.00-9.21	0.00	0.00
	Order HIV test	0.34-2.80	0.34	0.34
	Collect specimen	0.35-1.91	0.35	0.35
	Process HIV test§	1.24-1.29	1.24	1.04
	Document results (non-reactive)	0.00-0.59	0.00	0.00
	Deliver results (non-reactive)	0.00-1.49	0.00	0.00
	Document and deliver results (reactive)	17.13-22.44	17.13	7.93
	Perform HIV confirmatory testing§§	3.36-19.20	3.36	2.80
	Link to care	10.36-16.30	10.36	10.36
Materials				
	HIV testing§	9.12-9.59	9.12	9.12
	HIV confirmatory testing§§	40.71-41.29	40.71	40.25
	Link to care	0.00-0.36	0.00	0.00
Total				
	HIV test result (non-reactive)	17.00-23.83	11.05	10.85
	HIV test result (reactive)	89.29-109.52	82.61	72.19

ED = emergency department

Note: all costs are incremental.

†if cost equals zero, step was automated with no incremental cost

††only one ED had a cost for this step; at all other EDs this step was integrated into the registration process with no additional labor time required

§includes 4th generation laboratory testing cost only

§§includes Multispot confirmatory testing cost only

Conclusions: Expanded laboratory HIV testing was implemented in 4 EDs at a cost of approximately $17-$24 per completed non-reactive test (before overhead). An optimized process could achieve additional cost savings, but would require investments in interfaces between laboratory and electronic medical records systems to further automate some process steps.

1114 Global Fund Cost Projections for Implementing WHO 2013 Guidelines

Obinna Onyekwena; Ade Fakoya; Michael Johnson; Michael Olszak-Olszewski; Mark Dybul
The Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland

Background: Although recent global cost estimates indicate overall investments needed for implementation of the World Health Organization 2013 consolidated ART guidelines, detailed financial estimates for individual countries are limited. The aim of this study was to estimate additional costs for the transition of Global Fund grants to implement ART eligibility recommendations of the new guidelines.

Methods: The thirty-two countries which represent 83% of current Global Fund country allocations for HIV were included in the review. Data on treatment targets, ARV costs, and financing contributions to ARV were extracted from the Global Fund reporting database, grant documents and National AIDS Spending Assessment reports. Global projections for additional numbers of persons eligible for treatment, reported by WHO, were applied to country treatment targets to derive country-level number projections for 2015 to 2017. A weighted average ARV cost was used to determine associated ARV cost projections. Due to inter-program variability, facility and adherence support costs were not included. Treatment numbers and cost projections were disaggregated by new eligibility criteria and compared to current total allocations for HIV.

Results: ARV medicine cost for 2014 Global Fund commitments in 32 countries was estimated to be $628 million for 5 million patients on antiretroviral treatment. Additional cost of ARV medicines expected from ART eligibility recommendations was projected to be US$695 million to the end of 2017, for an additional 1.7 million persons on treatment. Costs for implementation of Option B+ and treating all HIV positive children below the age of five were US$53 million and US$106 million respectively; while initiating HIV positive persons with a CD4 count between 350 and 500 cells per mm^3 and in serodiscordant relationships had estimated additional costs of US$294 million and US$242 million respectively. The total ARV medicine cost projections represented approximately 41% (US$2.6 billion) of the total HIV allocations projected from 2015 to 2017 for the 32 countries analysed.

Conclusions: ARV medicine scale up costs alone will account for a significant portion of HIV resources allocated by the Global Fund to national HIV programs. This does not take into account additional facility and adherence support costs needed for quality service delivery. Understanding differential cost data in the implementation of treatment guidelines should strengthen strategic investments and portfolio optimisation.

WEDNESDAY, FEBRUARY 25, 2015

Session P-Z2 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Modeling HIV Epidemiology

1115 Estimating the Number and Characteristics of Male-Male HIV Transmissions in the USA

Eli S. Rosenberg[1]; Jeremy Grey[1]; Gabriela Paz-Bailey[2]; H. Irene Hall[2]; Amy Lansky[2]; Jonathan Mermin[2]; Jacek Skarbinski[2]
[1]Emory University Rollins School of Public Health, Atlanta, GA, US; [2]Centers for Disease Control and Prevention, Atlanta, GA, US; [3]CDC, Atlanta, GA, US

Background: HIV transmission risk is primarily dependent on sexual and injection drug use behaviors and HIV viral load. Data on behaviors and viral suppression among HIV-infected men who have sex with men (MSM) can be used to estimate transmissions to uninfected male partners. These estimates are important for informing HIV prevention efforts, particularly the balance between the population-impact benefits of antiretroviral therapy (ART) for HIV-infected MSM versus pre-exposure prophylaxis (PrEP) for at-risk HIV-uninfected MSM.

Methods: Using weighted respondent-level data on risk behaviors and viral load of HIV-infected persons in the United States from the CDC National HIV Behavioral Surveillance System and Medical Monitoring Project, and population-size estimates from the National HIV Surveillance System, we developed a static, deterministic model to estimate the number of HIV transmissions in 2009 attributable to individuals at each step of the HIV care continuum, by attributes of those individuals and their partners. We estimated transmissions from HIV-infected MSM to male sexual partners, stratified by partner type (main versus casual).

Results: An estimated 592,100 HIV-infected MSM had 4,009,405 male partners in 2009, with 24,069 transmissions to 1,132,800 HIV-negative or unknown status anal intercourse (AI) partners. Overall, 78% of transmissions were in main AI partnerships. Per serodiscordant AI partnership, HIV acquisition risk was higher for main than for casual AI partners (9.80 vs 0.57 per 100, respectively). Furthermore, 71% of all transmissions were in main AI partnerships in which the infected partner was not receiving ART, even though they represented only 13% of serodiscordant AI partnerships. In contrast, casual serodiscordant AI partnerships of MSM not receiving ART represented 21% of transmissions and 73% of serodiscordant AI partnerships.

Table: Estimated HIV transmissions to HIV serodiscordant anal intercourse partners, stratified by antiretroviral therapy status of HIV-infected partners, United States, 2009

	HIV serodiscordant anal intercourse partnerships		HIV Transmissions		Per-serodiscordant anal intercourse partnership acquisition rates
	Percent	*(number)*	*Percent*	*(number)*	*Rate, per 100*
Not on antiretroviral therapy					
Main partnerships	13.1%	(147,853)	71.4%	(17,192)	11.63
Casual partnerships	73.2%	(829,381)	21.1%	(5,079)	0.61
On antiretroviral therapy					
Main partnerships	3.8%	(43,022)	6.3%	(1,509)	3.51
Casual partnerships	9.9%	(112,544)	1.2%	(289)	0.26

Conclusions: To reduce HIV incidence among MSM, focused efforts are needed to increase the percentage of HIV-infected MSM who are on ART and achieve viral suppression and the percentage of HIV-uninfected MSM in discordant relationships who receive PrEP. We estimate over 1.1 million serodiscordant male-male AI partnerships in the United States in 2009, defining an upper-bound for the number of partnerships involving HIV transmission risk. Targeting the relatively small number of main serodiscordant relationships for ART and PrEP may have a particularly high prevention yield.

1116 Acute HIV Infection Transmission Among People Who Inject Drugs in an Established Epidemic Setting

Daniel Escudero[4]; Caleb Weinreb[4]; Mark Lurie[4]; Kenneth Mayer[2]; Sandro Galea[3]; Samuel Friedman[5]; Brandon Marshall[4]

[1]Brown University, Providence, RI, US; [2]Fenway Health, Boston, MA, US; [3]Columbia University, New York, NY, US; [4]Brown University, Providence, RI, US; [5]National Development and Research Institutes, Inc, New York, NY, US

Background: Among people who inject drugs (PWID), little is known about the contribution of acute HIV infection (AHI) to incident infections. Understanding its role in overall transmission may be crucial to improving the effectiveness of prevention strategies. We constructed an agent-based model (ABM) to estimate the proportion of transmission events attributable to AHI within an established HIV epidemic among PWID.

Methods: The ABM was previously calibrated to reproduce the sociodemographics, risk behavior, and HIV epidemic trajectory observed in the New York metropolitan statistical area (MSA) population. Agents interact in a mixed, and dynamic sexual and injecting transmission network, representing a 100,000 population. Each agent has a unique, time-updated probability of acquiring or transmitting HIV determined by their risk behavior, partnerships, engagement in simulated prevention interventions (i.e., needle and syringe programs, HAART), and HIV disease stage. Using stochastic microsimulations, we catalogued transmission events based on the disease stage of the index agent to determine the proportion of infections transmitted during AHI (defined as the three month period following infection).

Results: The calibrated model was able to approximate the epidemic trajectory among PWID in the New York MSA observed between 1992 and 2012. PWID comprised 1.9% of the general population in 1992, which decreased to 1.4% by 2012. Average annual incidence over this period was 0.07% for the general population; among PWID, incidence peaked at 3.5% during 1993-94 with a low of 1.7% in 2006. By 2012, 50% of HIV-infected PWID had initiated HAART, of whom 60% were virologically suppressed. Over the entire period, AHI accounted for 19% of incident HIV cases among PWID, with the following period-specific estimates: 15% (1992-1996, pre-HAART), 16% (1997-2004), and 23% (2005-2012).

Conclusions: This study is the first to produce an estimate for the proportion of incident HIV infections attributable to AHI among PWID. Our model (which accounted for sexual and parenteral transmission, heterogeneous risk behavior, assortative mixing, and the expansion of HIV treatment and prevention interventions over the last two decades) produced AHI transmission estimates at the lower end of those previously published for non-drug-using populations, which may be due to our modeling of an established, declining epidemic. Further research and sensitivity analyses are needed to confirm these preliminary results.

1117 Decreasing Number of Undiagnosed HIV Infections in the Netherlands

Ard van Sighem[1]; Fumiyo Nakagawa[3]; Daniela De Angelis[4]; Chantal Quinten[5]; Daniela Bezemer[1]; Eline Op de Coul[2]; Matthias Egger[7]; Frank de Wolf[6]; Christophe Fraser[6]; Andrew N. Phillips[3]

[1]Stichting HIV Monitoring, Amsterdam, Netherlands; [2]National Institute for Public Health and the Environment, Bilthoven, Netherlands; [3]University College London, London, United Kingdom; [4]MRC Biostatistics Unit, Cambridge, United Kingdom; [5]Europen Centre for Disease Prevention and Control, Stockholm, Sweden; [6]Imperial College London, London, United Kingdom; [7]Institute for Social and Preventive Medicine, University of Bern, Bern, Switzerland

Background: Accurate estimates of the size of the HIV-infected population, including those not yet diagnosed, are important to understand the HIV epidemic and to plan interventions. We sought to estimate the number living with HIV as well as trends in the undiagnosed population, HIV incidence, and rate of diagnosis in the past 10 years.

Methods: We used a multi-state back-calculation model to estimate HIV incidence, time between infection and diagnosis, and the HIV-infected population by CD4 count strata. The model was fitted to national surveillance data on new HIV and AIDS diagnoses from the ATHENA observational HIV cohort in the Netherlands. Rates of progression between the different states (primary infection, CD4 cell count ≥500, 350-499, 200-349, or <200 cells/mm^3, and AIDS) were based on historical cohort data on untreated HIV-infected patients. Bootstrap techniques were used to calculate 95% confidence intervals (CI).

Results: By the end of 2013, 29200 (95% CI 28000-30400) individuals, of whom 23400 (22200-24600) were still alive, were estimated to have been infected with HIV since the start of the epidemic in the 1980s. Based on registered HIV cases in ATHENA, we estimated that 91% of these patients, approximately 21300 (20200-22400), were still living in the Netherlands; the remaining 9% were not in care anymore because they moved abroad or were lost to follow-up. According to the model, the number of undiagnosed HIV-infected individuals decreased from 5150 (4850-5500) in 2003 to 3400 (2500-4650) in 2013. Of the undiagnosed individuals in 2013, 23% (19-27) were estimated to have been infected for less than one year, 53% (49-56) for one to 5 years, and 24% (19-30) for more than 5 years; 53% (51-55) had CD4 counts <500 cells/mm^3. The annual number of new infections remained almost unchanged: 1060 (940-1200) in 2003, 1020 (890-1151) in 2008, and 860 (590-1260) in 2013. At the time of diagnosis, the estimated proportion of patients infected less than 2 years before their HIV diagnosis increased from 21% (18-23) in 2003 to 26% (22-31) in 2013, while the proportion infected less than 5 years before increased from 60% (57-63) to 67% (62-73).

Conclusions: The number of undiagnosed HIV infections in the Netherlands is decreasing, but still almost a quarter has been infected for more than five years. Much greater increases in diagnosis rates are likely to be needed for a more substantial decrease in the annual number of new infections.

THURSDAY, FEBRUARY 26, 2015

Session P-Z3 Poster Session **Poster Hall**

2:30 pm – 4:00 pm

Modeling the Impact of HIV Interventions

1118 Predicted Impact of Antiretroviral Treatment on Preventing New HIV Infections in 53 Low- and Middle-Income Countries With Large HIV Epidemics

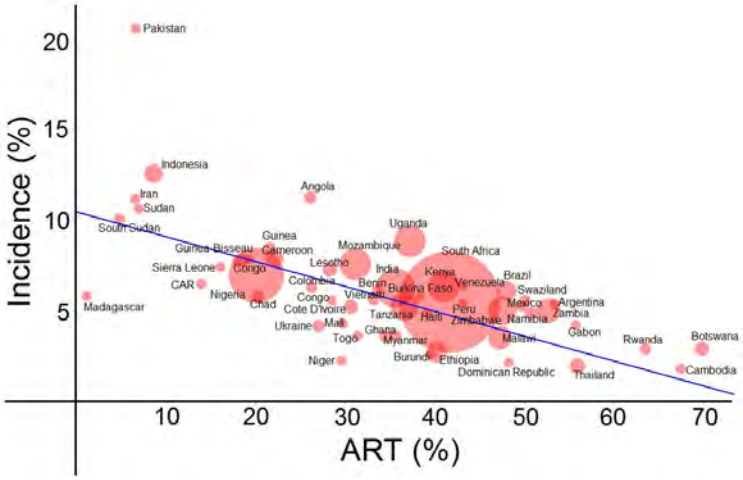
Andrew M. Hill[1]; Anton Pozniak[1]; Katherine Heath[2]; Alice Raymond[2]; Mary Mahy[3]; Nathan Ford[4]

[1]Chelsea and Westminster Hospital, London, United Kingdom; [2]St Mary's Hospital–Imperial College Healthcare NHS Trust, London, United Kingdom; [3]Joint United Nations Programme on HIV/AIDS (UNAIDS), Geneva, Switzerland; [4]World Health Organization, Geneva, Switzerland

Background: Clinical trials and observational studies have demonstrated that antiretroviral treatment can reduce the risk of HIV transmission. However, many countries still have low rates of antiretroviral treatment uptake.

Methods: Standardised epidemiological data were compiled from 36 African and 17 non-African low- and middle-income countries with least 40,000 HIV-infected people. Estimates of new HIV infections in 2013 by country were calculated using the AIDS Impact Module (AIM) in Spectrum. Each country entered HIV prevalence rates from pregnant women attending antenatal care or from key risk groups, the numbers receiving antiretroviral treatment, the numbers of pregnant women taking antiretroviral therapy (ART) to prevent vertical transmission, and the national antiretroviral eligibility criteria into the AIM. ART coverage rate was defined as the total number receiving ART divided by the epidemic size in each country. HIV transmission rate was defined as the number of new infections per year divided by the epidemic size in each country. Weighted least squares (WLS) regression was used to investigate the association between HIV transmission rates and antiretroviral treatment coverage across the 53 countries.

Results: An estimated 30.2 million people were infected with HIV in the 53 countries, among whom 11.0 million (36%) were receiving ART. However ART coverage rates ranged widely, from 1% in Madagascar to 70% in Botswana; 11/53 countries had <20% of HIV-infected people taking ART. In 2013, there were an estimated 1.81 million new HIV infections in these countries (mean HIV transmission rate=6%). The regression analysis showed that, for every 10% increase in antiretroviral treatment coverage there was approximately a 1.14% decrease in the HIV transmission rate. According to these analyses, if all 53 low and middle-income countries had had the same percentage of HIV-infected people taking antiretrovirals as Botswana (70%), 1.57 million of the 1.81 million total HIV infections in 2013 (87%) could have been prevented. The analysis was repeated using the 2014 Global Burden of Disease database, with similar results.



HIV Transmission rates versus ART coverage in 2013 by country

Conclusions: In these 53 low and middle-income countries with large HIV epidemics, there is the potential to prevent 1.57/1.81 million new HIV infections per year (87%) by increasing antiretroviral treatment coverage to levels already achieved by Botswana.

1119 Survival Benefits Attributable to the Brazilian National ART Policy

Paula M. Luz[1]; Michael P. Girouard[2]; Beatriz Grinsztejn[1]; Kenneth Freedberg[2]; Valdilea Veloso[1]; Elena Losina[4]; Claudio Struchiner[1]; Robert Parker[2]; David Paltiel[3]; Rochelle Walensky[2]

[1]Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil; [2]Massachusetts General Hospital, Boston, MA, US; [3]Yale School of Public Health, New Haven, CT, US; [4]Brigham and Women's Hospital, Boston, MA, US

Background: In Brazil, universal provision of antiretroviral therapy (ART) has been guaranteed free of charge to patients since 1996. We sought to quantify the survival benefits attributable to this policy.

Methods: We used a mathematical model of HIV disease (CEPAC-International) to estimate life expectancy of HIV-infected patients initiating ART between 1997 and 2013 in Brazil. We divided this timeframe into 5 eras, reflecting improvements in virologic and immunologic response to ART and in regimen sequencing over time. Input parameters were from the HIV Clinical Cohort at the Evandro Chagas Clinical Research Institute (Oswaldo Cruz Foundation) and from published Brazilian governmental data. Era-specific mean CD4 count at ART initiation ranged from 134/μL (Era 1) to 384/μL (Era 5). We included a loss to follow-up rate in each cohort of 10.1/1000 person-years. The 2014-censored and lifetime survival benefit attributable to each era were calculated as the sum of patients initiating ART in each cohort of a given era multiplied by the per-person survival increase attributable to ART in that era compared to pre-ART prophylaxis alone.

Results: In total, 556,829 individuals were estimated to have initiated ART in Brazil between 1997 and 2013 (Figure 1). Patients initiating ART in Era 1 had an estimated 2014-censored per-person life expectancy of 6.3 years compared to 2.9 years for pre-ART prophylaxis. Assuming no further improvements in care over time, projected lifetime per-person life expectancy increased from pre-ART (2.9 years) to 11.4, 17.0, 20.6, 23.7, and 25.7 years in Eras 1, 2, 3, 4, and 5, respectively. Total estimated population lifetime survival benefit for all persons starting ART from 1997 to 2013 in Brazil was 9.2 million life-years, with 1.3 million life-years realized as of 2014.

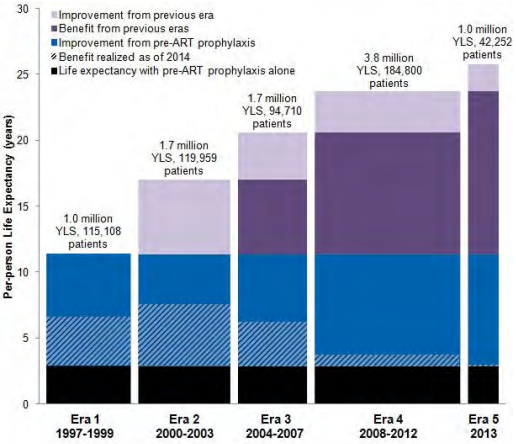


Figure 1. Years of life saved per person in each era produced by model simulations with a mean age at treatment initiation of 37 years (SD, 10 years). Bar width corresponds to the number of patients in each era and total colored area corresponds to lifetime survival benefits. Survival benefits realized as of 2014 are shaded with diagonal lines.

Conclusions: Brazil's national policy of free-of-charge ART access to patients has led to dramatic survival benefits, the vast majority of which have yet to be realized. Earlier HIV diagnosis, increased numbers accessing care, and improvements in ART regimens have all contributed substantially to these benefits.

1120 A Predictive Risk Model for First-Line Treatment Failure in South Africa

Julia K. Rohr[1]; Prudence Ive[2]; Rebecca H. Berhanu[2]; Kate Shearer[2]; Mhairi Maskew[2]; Lawrence Long[2]; Ian Sanne[2]; Matthew P. Fox[1]

[1]Boston University School of Public Health, Boston, MA, US; [2]University of Witwatersrand, Johannesburg, South Africa; [3]Right to Care, Johannesburg, South Africa

Background: Although individual predictors of first line antiretroviral therapy (ART) failure have been identified, few studies in resource-limited settings have been large enough for predictive modeling. Understanding the absolute risk of first line failure is useful for patient monitoring and for effectively targeting limited resources for second line ART. The aims of this study are to estimate absolute risk of failure of first line ART over 5 years on treatment as a function of key demographic, clinical, and immunologic factors at the start of ART, and to develop a predictive model that can be applied to other South African clinic populations.

Methods: This is an observational cohort study using medical records from 9 clinics across South Africa, including patients initiated on first line ART after 2004 with at least 6 months of follow-up time. The predictive model for virologic failure on first line (2 consecutive viral load levels >1000 copies/mL) was developed using accelerated failure time models (Weibull distribution), with stepwise selection of potential predictor variables at the start of ART. Multiple imputation was used to impute missing variables. The final predictive model was selected using an internal-external cross validation procedure using Harrell's C statistic to measure discrimination and difference between 5-year actual and predicted survival to measure calibration.

Results: 71,154 patients were included in the analysis, with an average of 21.5 months (IQR: 8.8-41.5) of follow-up time on first line ART. The final predictive model included age, sex, NNRTI on first line, baseline CD4 count, mean corpuscular volume, hemoglobin, history of tuberculosis, missed visits in the first 6 months on treatment, and an interaction between age and sex. Quintiles of the population were used to create 5 risk groups, where the highest risk group had 24.4% risk of failure over 5 years, and the lowest risk group had 9.4% risk of failure over 5 years. A simplified prognostic score to identify an individual's risk group was calculated directly from the model parameters (Table).

Table. Prognostic score calculation of risk group for virologic failure on first line ART.

Score calculation:		
1. Sex & age:		
Females:	Age:	
	18-24.9	8
	25-29.9	6
	30-34.9	4
	35-39.9	2
	40-44.9	1
	45+	0
Males:	Age:	
	18-24.9	7
	25-29.9	6
	30-34.9	5
	35-49.9	4
	50+	3
2. NNRTI:	NVP	3
	EFV	0
3. CD4 count:	0-25	10
	25-50	8
	51-100	6
	101-200	4
	201-350	2
	>350	0
4. MCV:	<80	0
	80-95	1
	95+	3
5. Hemoglobin:	<12	1
	12+	0
6. History of TB:	Yes	1
	No	0
7. Any missed visits during first 6 months on treatment:	Yes	4
	No	0

Score:	Risk group:	Predicted 5-year failure risk:
>17	High	24.4%
14-17	Medium-high	18.0%
12-13	Middle	14.8%
9-11	Medium-low	12.3%
0-8	Low	9.4%

Conclusions: The predictive model was able to discriminate between patients at higher risk of first line virologic failure. Identification of patients at highest risk of failure is useful for patient monitoring and referral for adherence counseling to improve patient outcomes and avoid the high cost of second line ART.

1121 U.S. Population Benefits of HIV Preexposure Prophylaxis for Injection Drug Users

Cora Bernard[1]; Margaret L. Brandeau[1]; Douglas K. Owens[2]; Keith Humphreys[2]; Eran Bendavid[1]; Mark Holodniy[2]; Christopher Weyant[1]; Jeremy D. Goldhaber-Fiebert[1]

[1]Stanford University, Stanford, CA, US; [2]VA Palo Alto Health Care System, Palo Alto, CA, US

Background: A Centers for Disease Control and Prevention (CDC)-sponsored randomized trial of daily oral preexposure chemoprophylaxis (PrEP) with Truvada demonstrated efficacy in preventing HIV infection among injection drug users (IDUs) in Thailand. CDC recommends PrEP for men who have sex with men (MSM) based on its effectiveness and cost-effectiveness. CDC also recommends considering PrEP for IDUs, though there are currently no estimates of PrEP's potential population health benefits for IDUs in the US.

Methods: We developed a dynamic model of HIV in the US for IDU, MSM, and lower risk groups that captured both sexual and injection transmission routes as well as preferential mixing between groups. The model used transition rates from the published literature and reflected current HIV prevalence and incidence, use of condoms and methadone maintenance therapy, HIV screening and awareness, and antiretroviral treatment (ART) rates consistent with CDC estimates for each risk group. For the period 2014-2034, we compared projections for two PrEP scenarios – PrEP efficacy as observed in the Thailand trial, PrEP half as efficacious as the trial – to projections for the status quo. We calculated projected HIV incidence and prevalence reductions in 2034 relative to the status quo for IDUs, as well as for MSM and lower risk groups not targeted by the intervention.

Results: Providing PrEP to all IDUs reduces HIV incidence and prevalence in IDUs by approximately 75% and 65%, respectively, an upper bound on population benefit. If efficacy is 50% of trial-reported levels, PrEP for all IDUs reduces HIV incidence and prevalence in IDUs by 50% and 43%. Because PrEP use includes frequent HIV screening, it substantially increases detection of new infections and the proportion of IDUs on ART. Through its effects on transmission, PrEP use in IDUs also reduces HIV incidence and prevalence in MSM

and lower risk groups but to a much smaller degree (<15%). Results depended on assumptions about PrEP coverage, adherence to PrEP, HIV screening on PrEP, and linking HIV awareness and ART uptake.

Conclusions: Widespread use of PrEP for IDUs in the US could substantially reduce HIV incidence and prevalence among IDUs and increase their HIV treatment rates. PrEP for IDUs would also benefit MSM and lower risk groups via reduced HIV transmission.

1122 Procreation in HIV-Serodiscordant Couples: TasP, PrEP, or Assisted Reproduction?

Guillaume Mabileau[1]; Michaël Schwarzinger[1]; Juan Flores[1]; Catherine Patrat[2]; Dominique Luton[2]; Sylvie Epelboin[2]; Laurent Mandelbrot[3]; Sophie Matheron[2]; Yazdan Yazdanpanah[2]
On behalf of ANRS 12008

[1]Inserm, Paris, France; [2]AP-HP, Bichat-Claude Bernard Hospital, Paris, France; [3]Louis Mourier Hospital, Colombes, France

Background: In the U.S., 2014 CDC guidelines based on expert recommendations have for the first time recommended PrEP as one of several options for fertile HIV-uninfected female/HIV-1-infected male couples on combination antiretroviral therapy (cART) with plasma HIV RNA <50 copies/mL desiring a child. However, in other Northern countries, medically assisted procreation (MAP) is still the recommended strategy. The aim of this study was to assess residual risk of HIV transmission, cost, and cost-effectiveness (CE) of various strategies that can help fertile HIV serodiscordant couples to have a child: (i) unprotected sexual intercourse (TasP); (ii) TasP limited to fertile days (FertilD); (iii) TasP with pre-exposure prophylaxis (PrEP) (tenofovir/emtricitabine); (iv) strategy (ii) + PrEP limited to fertile days; (v) medically assisted procreation (MAP).

Methods: We used a decision model. Input variables were from the international literature: 85% probability of live births in different strategies, 0.0083%/month HIV-transmission risk (β) with unprotected vaginal intercourse, 1% HIV mother-to-child transmission rate, and 4.4% birth defect risk related to cART when mother infected at conception. FertilD and PrEP were estimated to decrease β by 80% and 67%, respectively, and by 93.4% for PrEP+FertilD (1-(1-0.80)*(1-0.67)). Tenofovir/emtricitabine monthly cost was at €540. The CE analysis was performed from the French societal perspective (2013 euros), with a 4% annual discount rate.

Results: The probability of transmission to the female partner was highest with unprotected sexual intercourse strategy and lowest for MAP, followed by PrEP during fertile period (Table). FertilD was associated with the lowest costs and dominated PrEP, which was less effective with the highest costs. PrEP+FertilD cost-effectiveness ratio was €1,130,000/life year saved (LYS) when compared with FertilD; €3,600,000/LYS for MAP when compared with PrEP+FertilD. Results were robust to multiple sensitivity analyses.

Reproductive strategy assessed at one year for 10,000 HIV-serodiscordant couples	HIV-infected women/10,000 pregnancies	HIV-infected babies/10,000 pregnancies	Life expectancy* (undiscounted)	Life expectancy* (3% discount rate)	Costs (4% discount rate)	Incremental CE ratio (€/Life year saved)
FertiD	0.9	0.002	113.046	40.408	€ 785.90	--
TasP (baseline)	5.4	0.014	113.030	40.404	€ 786.67	Dominated
PrEP+FertilD	0.3	0.001	113.049	40.409	€ 1,324.29	1,128,000
MAP	0.0	0.000	113.050	40.409	€ 3,207.79	3,595,000
PrEP	1.8	0.005	113.043	40.408	€ 3,836.32	Dominated

* Life expectancy of both woman and child, woman being 33 years of age (113.046 = LE woman = 44.199 + LE baby = 68.847), rounded to three decimal places.

Conclusions: In fertile HIV-uninfected female/HIV-1-infected male couples with plasma HIV RNA <50 copies/mL, targeting fertile days lead to a low risk of HIV transmission. Considering PrEP during fertile period or MAP were found to decrease the risk of infections but these strategies were associated with unfavorable CE ratio.

DISCLOSURE INFORMATION

Disclosure information is presented as submitted by the corresponding author.

The authors listed below are the contact author for their presentations and have provided all relevant disclosures for themselves, their spouses, and their institution. In the event that an alternate author will be making the presentation, all relevant disclosures have also been provided for the alternate author, the alternate author's spouse, and the alternate author's institution.

Alland, David
Self: Cepheid: Grants/grants pending; Cepheid: Royalties
Institution: Rutgers University: Cepheid: Royalties

Amico, Rivet
Self: Gilead: Grants/grants pending

Arenas-Pinto, Alejandro
Self: Janssen: Payment for development of education presentations; Janssen: Grants/grants pending; BMS: Grants/grants pending
Institution: MRC-Clinical Trials Unit at UCL: Janssen: Provision of medicines, equipment, or administrative support; AbbVie: Provision of medicines, equipment, or administrative support; GSK: Provision of medicines, equipment, or administrative support; Gilead: Provision of medicines, equipment, or administrative support; Merck: Provision of medicines, equipment, or administrative support; Abbot Labs: Provision of medicines, equipment, or administrative support

Bandera, Alessandra
Self: Gilead: Grants/grants pending
Institution: S. Gerardo Hospital, Infectious Diseases Unit: AbbVie/Astellas/BMS: Grants/grants pending; Janssen/MSD: Grants/grants pending; Boehringer/Gilead: Grants/grants pending; ViiV Healthcare: Grants/grants pending; Novartis: Grants/grants pending; Roche: Grants/grants pending

Basilissi, Matteo
Institution: Department of Health Sciences, Clinical of Infectious Diseases and Tropical Medicine, San Paolo Hospital, Milan : Gilead Sciences Srl: Grants/grants pending

Baugher, Amy
Self: Oak Ridge Institute for Science and Education: Employment

Benarous, Richard
Self: Benarous Richard: Biodim Mutabilis: Employment
Institution: Biodim Mutabilis: Board Membership

Bennett, Sean
Self: Gilead Sciences Inc: Employment ; Other: Clinical trial agreement

Berenguer, Juan
Self: AbbVie: Consulting or advisor fee; BMS: Consulting or advisor fee; Gilead: Consulting or advisor fee; Janssen: Consulting or advisor fee; MSD: Consulting or advisor fee; ViiV: Grants/grants pending

Berg, Michael
Self: Abbott Laboratories: Employment

Bernardino, Jose
Self: Gilead: Consulting or advisor fee; ViiV healthcare: Consulting or advisor fee; MSD: Consulting or advisor fee; Janssen: Consulting or advisor fee; BMS: Consulting or advisor fee

Bhattacharya, Debika
Self: Bristol Myers Squibb: Other; AbbVie: Other

Bichoupan, Kian
Self: Janssen: Consulting or advisor fee

Blaschke, Terrence
Self: Durect Corporation: Board Membership; MWV Healthcare: Other; Proteus Digital Health: Consulting or advisor fee; Guthy Jackson Charitable Foundation: Consulting or advisor fee

Boeree, Martin
Institution: University of Munich: Sequella: Provision of medicines, equipment, or administrative support

Boesecke, Christophe
Self: AbbVie, BMS, Gilead, MSD, Janssen, ViiV: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus

Boffito, Marta
Self: BMS: Consulting or advisor fee; ViiV: Consulting or advisor fee; ViiV: Grants/grants pending; Gilead: Payment for development of education presentations; Gilead: Consulting or advisor fee; Janssen: Consulting or advisor fee

Boyd, Mark
Self: AbbVie: Grants/grants pending; Gilead Sciences: Board Membership; Merck: Grants/grants pending; Janssen-Cilag: Payment for development of education presentations; Bristol Myers Squibb: Payment for development of education presentations; Boehringer Ingelheim: Payment for development of education presentations

Brady, Kathleen
Self: Gilead: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus; Gilead Sciences: Grants/grants pending

Brew, Bruce
Self: ViiV Healthcare Australia: Grants/grants pending; ViiV Healthcare Australia: Payment for development of education presentations

Brown, Robert
Self: AbbVie, BMS, Gilead, Janssen, Merck: Grants/grants pending; AbbVie, BMS, Gilead, Janssen, Merck: Consulting or advisor fee

Brown, Todd
Self: AbbVie: Consulting or advisor fee; Merck: Board Membership; Gilead: Consulting or advisor fee; ViiV Healthcare: Consulting or advisor fee; EMD-Serono: Board Membership; Theratechnologies: Consulting or advisor fee

Butt, Adeel
Self: Merck, Gilead: Grants/grants pending

Callebaut, Christian
Self: Gilead: Employment; Gilead: Stock/stock options

Cashin, Kieran
Self: ViiV Healthcare: Other: honoraria from ViiV Healthcare Australia for conference travel

Castel, Amanda
Self: Gilead Sciences: Stock/stock options

Castillo-Mancilla, Jose
Self: Other: Study drug and contract work

Ceccherini-Silberstein, Francesca
Self: Merck Sharp & Dohme: Grants/grants pending; Merck Sharp & Dohme, ViiV Healthcare, Gilead : Consulting or advisor fee; ViiV Healthcare - Roche - Gilead - Janssen - AbbVie - Merck Sharp & Dohme: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus

Chow, Felicia
Self: AbbVie: Other

Colby, Donn
Self: Roche Molecular Systems: Grants/grants pending
Institution: Thai Red Cross AIDS Research Center: Merck: Provision of medicines, equipment, or administrative support; Cooper Human Systems: Grants/grants pending; Crucell: Grants/grants pending; Provision of medicines, equipment, or administrative support; Gilead: Provision of medicines, equipment, or administrative support

Cooper, David
Self: Gilead: Other; ViiV Healthcare: Other; Merck Sharp & Dohme: Other
Institution: UNSW: Gilead: Other; ViiV Healthcare: Other; Merck Sharp 7 Dohme: Other

Cowan, Frances
Self: Gilead Sciences: Provision of medicines, equipment, or administrative support

Crowley, Jeffrey
Self: Gilead Sciences: Grants/grants pending; AbbVie: Grants/grants pending; Bristol Myers Squibb: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus; WebMD: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus

Cuffe, Robert
Self: ViiV Healthcare: Employment; GlaxoSmithKline: Stock/stock options; Other: ViiV markets some of the drugs analyzed in the presentation. GSK has a majority shareholding in ViiV

Custodio, Joseph
Self: Gilead Sciences, Inc.: Stock/stock options
Institution: Gilead Sciences, Inc.: Gilead Sciences, Inc.: Employment

Cuzin, Lise
Self: Board Membership; ViiV Healthcare: Board Membership

Cysique, Lucette
Self: ViiV Healthcare: Grants/grants pending; AbbVie: Grants/grants pending; MSD: Grants/grants pending; AbbVie: Payment for development of education presentations

De Groote, Mary
Self: SomaLogic, Inc.: Consulting or advisor fee
Spouse/partner: SomaLogic, Inc: Employment

Dicker, Ira
Self: Bristol Myers Squibb: Employment

Dore, Gregory
Self: Gilead, AbbVie, Merck, Bristol-Myers Squibb, Janssen: Board Membership; Gilead, AbbVie, Merck, Bristol-Myers Squibb, Janssen: Grants/grants pending; Gilead, Merck, Roche, Janssen: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus; Gilead, AbbVie, Merck, Bristol-Myers Squibb: Other

Doyle, Tomas
Self: ViiV Healthcare: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus; Merck Sharpe & Dohme: Other: Merck Sharp and Dohme funded the study

Eckard, Allison
Self: GSK, BMS, Cubist Pharmaceuticals: Grants/grants pending; Gilead: Consulting or advisor fee; Other: data safety monitoring board section

Edén, Arvid
Self: Gilead, AbbVie, BMS, Roche: Other: travel grants; coauthor Dr Gisslén: lecture honoraria.

Elion, Richard
Self: Gilead Sciences, Merck, VIV, Jansen: Grants/grants pending; Gilead Sciences: Expert Testimony; Gilead Sciences, VIV, Merck, Jansen, BMS: Grants/grants pending; Gilead Sciences, ViiV, BMS : Consulting or advisor fee
Institution: Whitman Walker Health: Gilead Sciences: Grants/grants pending

Ferretti, Francesca
Institution: San Raffaele Scientific Institute: Bristol Meyer Squibb: Grants/grants pending

Fordyce, Marshall
Self: Gilead Sciences, Inc.: Employment

Foster, Rosalind
Self: Other: Research Funding

Galli, Laura

San Raffaele Scientific Institute: Bristol-Myers Squibb: Grants/grants pending

Gandhi, Monica
Self: Other: Gilead Sciences (South San Francisco, CA) provided TDF/FTC in iPrEX OLE but had no other role in study design, data accrual and analysis, or abstract preparation.

Gange, Stephen
Self: Merck, Inc.: Fees for participation in the review activities, eg, data monitoring boards, statistical analysis, or end point adjudication committees

German, Polina
Self: Gilead Sciences, Inc.: Employment; Stock/stock options

Gibb, Diana
Institution: University College London: ViiV Healthcare, Merck, Gilead, CIPLA for supply of drugs for clinical trials: Provision of medicines, equipment, or administrative support

Golden, Matthew
Self: Melinta Pharmaceuticals: Grants/grants pending

Gottlieb, Geoffrey
Self: Alere Technologies, GmbH: Grants/grants pending; Gilead Sciences, Inc: Grants/grants pending; BMGF: Grants/grants pending; UptoDate: Royalties; Monogram Biosciences: Grants/grants pending; Abbott: Provision of medicines, equipment, or administrative support

Grant, Robert
Self: Gilead Sciences: Provision of medicines, equipment, or administrative support; ViiV: Grants/grants pending; Siemens: Consulting or advisor fee

Grinspoon, Steven
Self: Theratechnologies: Consulting or advisor fee; Navidea: Consulting or advisor fee; Novo Nordisk: Consulting or advisor fee; Astra Zeneca: Consulting or advisor fee
Institution: Amgen: Grants/grants pending; Grants/grants pending; Theratechnologies: Grants/grants pending; Bristol-Myers Squibb: Grants/grants pending

Grulich, Andrew
Self: ViiV, Gilead: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus

Gupta, Samir
Self: Janssen Therapeutics: Grants/grants pending; Gilead Sciences: Grants/grants pending; Merck & Co: Grants/grants pending

Hakim, James
Self: Mylan Pharmaceuticals: Board Membership

Ham, Anthony
Self: ImQuest BioSciences: Stock/stock options
Institution: NIH: Grants office: Grants/grants pending
Spouse/partner: ImQuest BioSciences: Employment

Hamzah, Lisa
Self: Janssen-Cilag: Payment for development of education presentations; Gilead Sciences: Lisa Hamzah has received funding from Gilead Sciences to attend a conference. Coauthor Frank A. Post has received funding to attend conferences or educational meetings, honoraria and/or research funding from AbbVie, Gilead Sciences, Bristol-Myers Squibb, Janssen-Cilag, GlaxoSmithKline/ViiV Healthcare and Merck

Hill, Andrew
Self: Janssen: Consulting or advisor fee; Diego Ripamonti: Consulting or advisor fee; Ralph DeMasi: Employment; Ceyhun Bicer: Employment; Christiane Moecklinghoff: Employment; Graham Cooke: Gilead: Consulting or advisor fee

Ho, Emily
Self: Santa Cruz Biotechnology, Inc.: Royalties

Huang, Wei
Self: Monogram Biosciences: Employment

Huang, Yunda
Self: Bionor Pharma ASA: Consulting or advisor fee

Hullegie, Sebastian
Institution: Erasmus MC: Merck, Gilead: Grants/grants pending

Hunt, Peter
Self: Consulting or advisor fee; Bristol Myers Squibb: Consulting or advisor fee; Gilead: Consulting or advisor fee; Gilead: Payment for development of education presentations; Janssen: Payment for development of education presentations; Tobira: Consulting or advisor fee

Ingiliz, Patrick
Self: Gilead: Board Membership; AbbVie: Board Membership; Janssen-Cilag: Payment for development of education presentations; BMS: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus

Jain, Vivek
Self: Gilead Sciences: Grants/grants pending

Jeffrey, Jerry
Self: GSK: Employment

Kim, Arthur
Self: Bristol-Myers Squibb: Consulting or advisor fee; AbbVie: Consulting or advisor fee
Institution: Massachusetts General Hospital: AbbVie: Grants/grants pending; Gilead Sciences: Grants/grants pending

Klein, Marina
Self: GlaxoSmithKline/ViiV: Consulting or advisor fee; Merck: Grants/grants pending; Schering-Plough: Grants/grants pending; Bristol-Myers Squibb: Grants/grants pending; Gilead: Payment for development of education presentations; GlaxoSmithKline/ViiV: Payment for development of education presentations

Klevens, Monina
Self: CDC Foundation: Provision of medicines, equipment, or administrative support; Other: Data purchase from Quest and administrative support to analyze data were funded with a grant from the CDC Foundation which currently receives a grant from AbbVie

Kohli, Payal
Self: Amgen: Consulting or advisor fee; Pfizer: Consulting or advisor fee; Summer Street Research: Consulting or advisor fee

Kooij, Katherine
Self: Gilead Sciences: Other: Through my institution I have received a travel grant to attend a scientific conference from Gilead Sciences

Koss, Catherine
Institution: University of California, San Francisco: AbbVie Pharmaceuticals: Provision of medicines, equipment, or administrative support; Other: AbbVie Pharmaceuticals (North Chicago, Illinois) provided lopinavir/ritonavir (Aluvia) but had no other role in study design, data accrual and analysis, or abstract preparation

Kostman, Jay
Self: AbbVie: Consulting or advisor fee

Krakower, Douglas
Self: Gilead Sciences: Grants/grants pending; Bristol-Myers Squibb: Grants/grants pending; Medscape: Payment for development of education presentations

Landovitz, Raphael
Self: Gilead Sciences: Consulting or advisor fee; Gilead Sciences: Provision of medicines, equipment, or administrative support
Institution: UCLA: Gilead: Provision of medicines, equipment, or administrative support; Bristol-Myers Squibb: Provision of medicines, equipment, or administrative support; GlaxoSmithKline/ViiV: Provision of medicines, equipment, or administrative support; Janssen Therapeutics: Provision of medicines, equipment, or administrative support

Landry, Ishani Savant
Self: Bristol-Myers Squibb: Employment; Stock/stock options
Institution: Bristol-Myers Squibb: Patents(planned, pending, or issued); Other: Bristol-Myers Squibb is a commercial entity, patenting and developing the drug described within this presentation

Larsen, Ellen
Self: Gilead: Grants/grants pending

Lataillade, Max
Self: Bristol-Myers Squibb: Employment; Stock/stock options
Institution: Bristol-Myers Squibb: Employment; Stock/stock options; Other

Lee, Frederick
Self: Calimmune Australia Pty Ltd: Consulting or advisor fee; Janssen Cilag Australia: Grants/grants pending

Lee, Samuel
Self: Bristol-Myers Squib, Boehringer Ingelheim, Debio, Gilead, Janssen, GlaxoSmithKline, Merck, Novartis, Roche, Vertex: Other; BMS, Gilead, Janssen, Merck, Roche, Vertex.: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus

Leroy, Valeraine
Self: EDCTP, ANRS, CRP Santé: Grants/grants pending

Letendre, Scott
Self: AbbVie: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus; ViiV Healthcare: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus; Gilead Sciences: Grants/grants pending; GlaxoSmithKline: Grants/grants pending; AbbVie: Grants/grants pending

Lichtenstein, Kenneth
Self: AbbVie Pharmaceuticals: Grants/grants pending

Luetkemeyer, Anne
Self: Cepheid: Grants/grants pending
Institution: UCSF: Cepheid: Grants/grants pending

Margolis, David
Self: GSK: Employment

Marks, Kristen
Self: Gilead: Grants/grants pending; Merck: Grants/grants pending; BMS: Grants/grants pending; BI: Grants/grants pending; Vertex: Grants/grants pending

Mauss, Stefan
Self: Gilead: Consulting or advisor fee; AbbVie: Consulting or advisor fee; Janssen: Consulting or advisor fee; Roche: Consulting or advisor fee; BMS: Consulting or advisor fee

Mayer, Kenneth
Self: Gilead Sciences: Grants/grants pending

McComsey, Grace
Self: Bristol-Myers Squibb, GSK/ViiV, Gilead: Grants/grants pending; Other; Gilead, GSK, Consulting or advisor fee; Merck: Other; Pfizer: Fees for participation in the review activities, eg, data monitoring boards, statistical analysis, or end point adjudication committees

McCormack, Sheena
Self: Gilead Sciences plc: Grants/grants pending; Gilead Sciences plc: Provision of medicines, equipment, or administrative support
Institution: MRC CTU at UCL (Infections Group): Abbott, BMS, Cipla, Gilead, Tibotec, Roche, GSK, Janssen-Cilag, Merck: Provision of medicines, equipment, or administrative support; MRC CTU at UCL (Infections Group): Abbott, BMS, Gilead, Tibotec, Roche, GSK, Janssen-Cilag, Merck: Grants/grants pending
Spouse/partner: BXT Accelyon: Other

Mercie, Patrick
Self: Gilead: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus; Mercie: B: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus; Mercie: Pfizer: Provision of medicines, equipment, or administrative support

Miller, Michael
Self: Merck & Co., Inc.: Employment
Institution: Merck & Co., Inc.: Merck & Co., Inc: Employment
Spouse/partner: Merck & Co., Inc.: Employment

Molina, Jean-Michel
Self: Gilead: Board Membership; Merck: Board Membership; Janssen: Board Membership; ViiV: Board Membership; Bristol-Myers Squibb: Board Membership
Institution: Hopital Saint-Louis: Gilead: Grants/grants pending

Monroe, Anne
Institution: John Hopkins University: NIH: Grants/grants pending

Naggie, Susanna
Self: Gilead Sciences, Inc: Consulting or advisor fee; Bristol Meyers Squibb: Consulting or advisor fee; Merck: Consulting or advisor fee; AbbVie: Consulting or advisor fee
Institution: Duke University: Gilead: Grants/grants pending; Bristol Meyers Squibb: Grants/grants pending; AbbVie: Grants/grants pending; Vertex: Grants/grants pending; Duke Clinical Research Institute: Gilead: Grants/grants pending; Durham VA Medical Center: AbbVie: Grants/grants pending
Spouse/partner: BTG, International Incorporated: Grants/grants pending

Naqvi, Alissa
Self: Gilead Sciences: Board Membership

Noy, Ariela
Institution: Memorial Sloan Kettering Cancer Center: Pharmacyclics: Other

O'Halloran, Jane
Self: Janssen Cilag: Other
Institution: University College Dublin: Janssen Cilag: Grants/grants pending; GlaxoSmithKline: Grants/grants pending; Gilead Sciences: Grants/grants pending; Bristol-Myers Squibb: Grants/grants pending; Merck: Grants/grants pending; Other: Education grants to facilitate travel to and conference registration

Palella, Frank
Self: Janssen Pharmaceuticals, Bristol Myers Squibb, Merck, Gilead Sciences: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus

Parkes-Ratanshi, Rosalind
Self: Janssen Pharmaceuticals: Consulting or advisor fee
Institution: Infectious Diseases Institute: Janssen Pharmaceuticals: Consulting or advisor fee

Paton, Nicholas
Self: GSK: Grants/grants pending; AbbVie: Other; Janssen: Other; Nicholas Paton has received payment as a speaker for AbbVie and Janssen. Other: the primary presenter has received honoraria for speaking at symposia organized by the two companies listed.
Institution: National University of Singapore: GSK: Grants/grants pending; : GSK: Provision of medicines, equipment, or administrative support

Perreau, Matthieu
Self: Bristol Myers Squibb: Grants/grants pending

Peters, Marion
Self: Biotron: Consulting or advisor fee
Spouse/partner: Genentech Research and Development: Employment

Peytavin, Gilles
Self: Bristol-Myers-Squibb, Gilead Sciences, Janssen, Merck and ViiV Healthcare: Board Membership; Gilead Sciences, Janssen, Merck and ViiV Healthcare: Consulting or advisor fee; Grants/grants pending; Gilead Sciences, Janssen, Merck and ViiV Healthcare: Payment for development of education presentations

Piroth, Lionel
Self: BMS: Consulting or advisor fee; Gilead: Consulting or advisor fee; Pfizer: Consulting or advisor fee; ViiV Healthcare: Consulting or advisor fee

Polizzotto, Mark
Self: Celgene Corporation: Provision of medicines, equipment, or administrative support
Institution: National Cancer Institute: Celgene Corporation: Provision of medicines, equipment, or administrative support ; Other: Research Funding, Celgene Corporation

Porter, Danielle
Self: Gilead Sciences, Inc.: Employment

Quirk, Erin
Self: Gilead Sciences: Employment; Gilead Sciences: Stock/stock options; Other: clinical trial agreements

Ramers, Christian
Self: Gilead Sciences, AbbVie, ViiV, Janssen: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus

Ramgopal, M
Institution: Midway Immunology and Research Center: Janssen: Grants/grants pending

Raugi, Dana

Other: Monogram Biosciences - Research support

Rice, Charles
Self: Apath, LLC: Other; Merck: Consulting or advisor fee; OnCore: Board Membership; Regeneron: Consulting or advisor fee

Roederer, Mario
Self: FlowJo, LLC: Other

Rokx, Casper
Self: ViiV Healthcare, outside submitted work.: Grants/grants pending

Rourke, Sean
Self: AbbVie: Other

Ruel, Theodore
Institution: University of California, San Francisco: AbbVie: Provision of medicines, equipment, or administrative support; Other: AbbVie Pharmaceuticals (North Chicago, Illinois) provided lopinavir/ritonavir (Aluvia) but had no other role in study design, data accrual and analysis, or abstract preparation

Sax, Paul
Self: Gilead: Consulting or advisor fee; AbbVie: Consulting or advisor fee; GSK/ViiV: Consulting or advisor fee; Merck: Consulting or advisor fee; BMS: Consulting or advisor fee; Janssen: Consulting or advisor fee

Sekaly, Pierre-Rafick
Self: Caprion: Consulting or advisor fee
Institution: Case Western Reserve University: Medimmune: Grants/grants pending; Gilead: Grants/grants pending; Sanofi: Grants/grants pending; Sangamo: Grants/grants pending

Siccardi, Marco
Self: Janssen: Grants/grants pending; Saye Khoo: Janssen: Grants/grants pending; David Back: Janssen: Grants/grants pending; Andrew Owen: Janssen: Grants/grants pending

Sigel, Keith
Self: Gilead Sciences: Consulting or advisor fee

Sloan, Derek
Self: Gilead Sciences, Inc.: Employment

Sohn, Annette
Institution: amfAR, the Foundation for AIDS Research: ViiV Healthcare: Grants/grants pending; grant to my institution is unrelated to the work under consideration and is for research and training

Spagnuolo, Vencenzo
Institution: Infectious Diseases Department, San Raffaele Scientific Institute: Bristol Myers Squibb: Grants/grants pending

Sterling, Timothy
Self: Otsuka: Other: Data safety monitoring board for a TB clinical trial

Sulkowski, Mark
Self: Achillion, AbbVie, BMS, Gilead, Merck, Janssen: Consulting or advisor fee
Institution: Johns Hopkins University: AbbVie, BMS, Gilead, Janssen: Grants/grants pending; Gilead : Fees for participation in the review activities, eg, data monitoring boards, statistical analysis, or end point adjudication committees

Swenson, Eugene
Self: Bristol-Myers Squibb: Employment

Taiwo, Babafemi
Self: ViiV: Grants/grants pending; ViiV: Consulting or advisor fee; Gilead: Consulting or advisor fee; Pfizer: Grants/grants pending

Tang, Winson
Self: Sangamo BioSciences: Employment

Tazi, Jamal
Self: ABIVAX: Consulting or advisor fee
Institution: University of Montpellier: Abivax: Grants/grants pending

Thompson, Melanie
Self: Janssen/Tibotec Therapeutics: Fees for participation in the review activities, eg, data monitoring boards, statistical analysis, or end point adjudication committees; ViiV Healthcare: Fees for participation in the review activities, eg, data monitoring boards, statistical analysis, or end point adjudication committees
Institution: All are research contracts (not grants). Additional disclosures for institution, AIDS Research Consortium of Atlanta: Pfizer, Inc., Janssen/Tibotec Therapeutics, Merck, Tobira Therapeutics, ViiV Healthcare. All are research contracts. Bristol-Myers Squibb disclosures: Bristol-Myers Squibb is a commercial entity, patenting and developing the drug described within this presentation

Tolstrup, Martin
Self: Aarhus University has filed a patent on the use of panobinostat in HIV-infected individuals on which I am co-inventor: Patents(planned, pending, or issued)

Tomaras, Georgia
Institution: Duke University: NIH BMGF: Other

van Sighem, Ard
Institution: Stichting HIV Monitoring: Gilead Sciences: Grants/grants pending; ViiV Healthcare: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus; Bristol-Myers Squibb: Payment directly from commercial firms for lecture(s), including service on speakers' bureaus

van Zyl, Gert
Self: AbbVie: Payment for development of education presentations

Vandamme, Anne-Mieke
Self: AbbVie: Payment for development of education presentations
Institution: KULeuven: mecenat program : Other
Spouse/partner: ViiV, AbbVie, Gilead: Payment for development of education presentations

Vavro, Cindy
Self: GlaxoSmithKline: Employment
Institution: GlaxoSmithKline: GlaxoSmithKline: Employment

Warszawski, Josiane
Self: Parexel: Other; ViiV Healthcare: Other: These disclosure do not concern the current work submitted, and consist in grants via contract with our promotor for pharmacoviligance studies

Wherry, E. John
Self: Genentech/Roche: Patents(planned, pending, or issued); Surface Oncology: Stock/stock options

Whitney, James
Self: Gilead: Grants/grants pending
Institution: Beth Israel Deaconess Medical Center: Gilead: Grants/grants pending

Wohl, David
Self: Gilead Sciences: Grants/grants pending; Gilead Sciences: Consulting or advisor fee; Janssen: Consulting or advisor fee
Institution: University of North Carolina: Merck: Grants/grants pending

Wong, Alexander
Self: Gilead Sciences, Inc.: Consulting or advisor fee; ViiV Healthcare: Consulting or advisor fee; Bristol-Myers Squibb: Consulting or advisor fee; Janssen Pharmaceuticals, Inc.: Consulting or advisor fee; Gilead Sciences, Inc.: Grants/grants pending; ViiV Healthcare: Grants/grants pending

Wong, Michael
Self: Sarepta Therapeutics : Employment

Wyles, David
Self: BMS: Consulting or advisor fee; AbbVie: Consulting or advisor fee; Gilead: Consulting or advisor fee; Janssen: Consulting or advisor fee; AbbVie, BMS, Gilead, Merck, Vertex Pharmaceuticals, Tacere Therapeutics (payable to UC): Grants/grants pending; AbbVie, BMS, Gilead, Janssen: Consulting or advisor fee
Institution: UCSD: Gilead, AbbVie, Merck, BMS, Tacere: Grants/grants pending

Yee, Ka Lai
Self: Merck & Co: Employment

Yeh, Wendy
Self: Merck & Co., Inc.: Employment

Yin, Michael
Self: Gilead: Consulting or advisor fee; AbbVie: Consulting or advisor fee

DISCLOSURE INFORMATION

The following have no relevant financial relationships to disclose:

Abassi, Mahsa
Abdel-Hameed, Enass
Abdel-Mohsen, Mohamed
Abraham, Alison
Abrams, Elaine
Achhra, Amit
Ackerman, Margaret
Adams, Joella
Adeyemi, Oluwatoyin
Agaba, Patricia
Agan, Brian
Agsalda-Garcia, Melissa
Agüero, Fernando
Ahlgren, Erika
Ahonkhai, Aimalohi
Ahrenstorf, Gerrit
Ajaykumar, Abhinav
Ake, Julie
Akiyama, Hisashi
Alam, Muntasir
Al-Harthi, Lena
Almirall, Daniel
Alter, Galit
Alteri, Claudia
Althoff, Keri
Aluzimbi, George
Alvarez, Angeles
Anderson, Elizabeth
Andrade, Viviane
Andreotti, Mauro
Anesten, Birgitta
Apondi, Rose
Apostolova, Nadezda
Appelberg, Sofia
Archary, Moherndran
Armeia, Daniele
Arpadi, Stephen
Asahchop, Eugene
Attia, Engi
Auld, Andrew
Aurpibul, Linda
Avelino-Silva, Vivian
Avihingsanon, Anchalee
Avila-Rios, Santiago
Aweeka, Francesca
Bade, Aditya
Bader, Joëlle
Baeten, Jared
Baggaley, Rachel
Bahr, Nathan
Baker, Laurie
Balagopal, Ashwin
Balaji, Alexandra
Balestre, Eric
Balkus, Jennifer
Ballana, Ester
Bar, Katharine
Baral, Stefan
Barlow-Mosha, Linda
Barouch, Dan
Bartha, István
Basco, Brian
Bassett, Ingrid
Batavia, Ashita
Baxi, Sanjiv
Becker, James
Bednar, Maria
Beisel, Claudia
Bekker, Linda-Gail
Belknap, Robert
Bendavid, Eran
Berhanu, Rebecca
Bernard, Cora
Best, Brookie
Bijker, Rimke
Bility, Moses
Birx, Ambassador Deborah
Blanco, José
Boender, Tamara Sonia
Boettiger, David
Bolouri, Hamid
Bolton, Diane
Boltz, Valerie
Bonczkowski, Pawel
Bonfanti, Paolo
Bor, Jacob
Borges, Álvaro
Bove, Joanna
Bowman, Natalie
Boyd, David
Boyd, Anders
Bradley, Heather
Braunstein, Sarah
Brenner, Bluma
Brew, Bruce
Brezar, Vedran
Briggs, Melissa
Brocca-Cofano, Egidio
Brodsky, Allison
Brooks, Katherine
Brouillette, Marie-Josée
Browne, Sara
Brumme, Chanson
Buchacz, Kate
Buchbinder, Susan
Bucher, Heiner
Buechler, Matthew
Bull, Marta
Burch, Lisa
Burgener, Adam
Burgos, Joaquin
Buseyne, Florence
Bushman, Frederic
Buskin, Susan
Bussmann, Hermann
Butler, Karina
Byakwaga, Helen
Cabrera, Cecilia
Calcagno, Andrea
Calderon, Monica
Calenda, Giulia
Calvert, Clara
Camacho-Gonzalez, Andres
Campbell, Grant
Casazza, Joseph
Cassol, Edana
Castilho, Jessica
Cesar, Carina
Chamie, Gabriel
Chan, Brian
Chang, Sui-Yuan
Charlebois, Edwin
Chavez, Pollyanna
Chen, Iris
Chen, Xinhui
Chew, Kara
Chohan, Bhavna
Chow, Dominic
Chowdhury, Ankita
Christ, Frauke
Cillo, Anthony
Cingolani, Antonella
Clement, Meredith
Coates, Thomas
Cockerham, Leslie
Coffin, John
Coghill, Anna
Cohen, Karen
Cohn, Silvia
Colasanti, Jonathan
Cope, Anna
Corbett, Elizabeth
Cori, Anne
Cournil, Amandine
Cozzi-Lepri, Alessandro
Crane, Heidi
Crespo, Manel
Cressey, Tim
Cross, Gail
Crowell, Trevor
Cummins, James
Curlin, Marcel
Dadaille, Rita
Dan, Jennifer
Danel, Christine
Dangarembizi, Mutsa Bwakura
Dansereau, Emily
Dash, Prasanta
Daughtridge, Giffin
Day, Tyler
de Armas, Lesley
de Oliveira, Tulio
de Pundert, Marieke
de Sousa Muhate, Amina
Deayton, Jane
Del Bello, David
Dela Cruz, Mark
Delagreverie, Heloise
Delaney, Kevin
DeMaster, Laura
Deryabina, Anna
Desai, Seema
Desai, Mitesh
Dirajlal-Fargo, Sahera
Dobard, Charles
Doitsh, Gilad
Dolan, Matthew
Dooley, Kelly
Drake, Alison
Drozd, Daniel
Dryden-Peterson, Scott
Duenas-Decamp, Maria
Duncan, Melanie
Dunne, Eileen
Durham, Natasha
Easterbrook, Philippa
Egger, Matthias
El-Diwany, Ramy
Elliott, Julian
Ellman, Tanya
Elopre, Latesha
El-Sadr, Wafaa
Ende, Zachary
Erdmann, Nathaniel
Erlandson, Kristine
Escudero, Daniel
Espinoza, Lorena
Espluges, Juan
Evering, Teresa
Faldetta, Kimberly
Fankuchen, Olivia
Faria de Oliveira, Michelli
Farzan, Michael
Fazeli, Pariya
Feldmann, Anna
Fievez, Virginie
Finn, Erin
Firnhaber, Cynthia
Fischer, Rebecca
Fischl, Margaret
Fiske, Christina
Fluharty, Tayler
Fogel, Jessica
Foissac, Frantz
Fortuny, Clàudia
Fouda, Genevieve
Fowler, Mary Glenn
Fox, Julie
Fox, Matt
Fraser, Christophe
Frater, John
Fregoso, Oliver

Freguja, Riccardo
French, Audrey
Fulcher, Jennifer
Fyne, Elizabeth
Gale, Michael
Gama, Lucio
Garcia, Felipe
García-Álvarez, Mónica
Garcia-Morales, Claudia
Gardner, Lytt
Garg, Ankita
Garg, Shikha
Garrido, Carolina
Gathogo, Esther
Gavegnano, Christina
Gebi, Usman
Geboy, Alexander
Geijtenbeek, Teunis
Gelman, Benjamin
Genberg, Becky
Gianella Weibel, Sara
Gianesin, Ketty
Gill, Michelle
Gill, Alexander
Gingo, Matthew
Glidden, David
Glynn, Judith
Goedert, James
Gogia, Shawn
Gonzalez-Serna, Alejandro
González-Tomé, María Isabel
Gooneratne, Shayarana
Gopal, Satish
Grabowski, Mary
Green, Nella
Greenblatt, Ruth
Guardo, Alberto
Guedj, Jérémie
Guerra, Vitor
Guillén, Yolanda
Guo, Dongwei
Gupta, Amita
Haaland, Richard
Haas, Andreas
Haberer, Jessica
Haidari, Goli
Hall, H. Irene
Ham, David
Hanifa, Yasmeen
Hanna, David
Harada, Shigeyoshi
Harper, Michael
Hassounah, Said
Hataye, Jason
Hatleberg, Camilla
Haughey, Norman
Hawkins, Claudia
Hechter, Rulin
Heffron, Renee
Hellar, Augustino
Hensley-McBain, Tiffany
Herbeck, Joshua
Herce, Michael
Hernández, Selma Alva
Hernandez-Romieu, Alfonso
Hesseling, Anneke
Hileman, Corrilynn
Ho, Ya-Chi
Hodcroft, Emma
Hodowanec, Aimee
Hoelscher, Michael
Hoenigl, Martin
Hofmann, Christian
Hofstra, Marije
Hogan, Joseph
Hong, Feiyu
Hontelez, Jan
Hood, Julia
Hoots, Brooke
Hoover, Karen
Hosein, Megan
Hosmane, Nina
Hove, Malene
Hsiao, Nei-Yuan
Hsieh, Evelyn
Hsieh, Yu-Hsiang
Hsieh, Anthony
Hsu, Denise
Huang, Szu-Wei
Huang, Billy
Huerga, Helena
Hughes, Stephen
Hulgan, Todd
Hunt, Peter
Ignacio, Rachel Bender
Ike, Ndidi
Ingle, Suzanne
Innes, Steve
Ita-Nagy, Fanny
Ivy, Wade
Iyer, Shilpa
Jackson, Patrick
Jacobsen, Jefrey
Jacobson, Denise
Jain, Prashant
Jao, Jennifer
Jaquet, Antoine
Jarrin, Inma
Jaumdally, Shameem
Jensen, Kara
Jerome, Keith
Jia, Manxue
Jiang, Wei
Jimmerson, Leah
Johnson, Phil
Johnson, Erica
Johnson, Phil
Joseph, Sarah
Joy, Jeffrey
Joyce, M. Patricia
Kaczmarek, Dominik
Kagaayi, Joseph
Kallianpur, Asha
Kambugu, Andrew
Kandathil, Abraham
Karat, Aaron
Karchava, Marika
Karmon, Sharon
Katz, David
Katz, Ingrid
Kearney, Mary
Kebaya, Lilian
Kekitiinwa, Adeodata
Keller, Marla
Kelley, Colleen
Kelly, Sean
Kenney, Shannon
Kenny, Julia
Kersh, Ellen
KewalRamani, Vineet
Khaitan, Alka
Khan, Palwasha
Khosropour, Christine
Khoury, Georges
Kiani, Zahra
Kibbie, Jon
Kijewski, Suzanne
Kilama, Bonita
Kim, Connie
King, Caroline
Kinloch, Sabine
Kirkpatrick, Allison
Kityo, Cissy
Kiwanuka, Noah
Klafter, Jesse Abbott
Klein, Katja
Knudsen, Troels Bygum
Koethe, John
Koh, Christopher
Kok, Yik Lim
Kokordelis, Pavlos
Kong, Xiangrong
Kong, Rui
Kostadinova, Lenche
Kourtis, Athena
Kovari, Helen
Krämer, Benjamin
Krebs, Shelly
Kreider, Edward
Krishnan, Supriya
Krogan, Nevan
Kroidl, Arne
Kuo, Irene
Kutscher, Hilliard
Kwakwa, Helena
Kwarisiima, Dalsone
Laanani, Moussa
Lacabaratz, Christine
Lachowsky, Nathan
Laeyendecker, Oliver
Laga, Marie
Laguette, Nadine
Laird, Gregory
Lancaster, Kathryn
Lane, H. Clifford
Langness, Jacob
Lattimore, Sam
Laut, Kamilla
Le, Thuy
Leal, Lorna
Ledwaba, Johanna
Lee, Ha Youn
Lee, Sulggi
Lee, Wingyiu
Leitman, Ellen
Leone, Sebastiano
Leong, Yew Ann
Leoz, Marie
Leroy, Valeriane
Lesko, Catherine
Leuenberger, David
Leung, Janice
Levin, Jonathan
Levine, Andrew
Levy, David
Li, Jonathan
Li, Peilin
Li, Zhe
Li, Duo
Libre, Camille
Lichtenstein, Kenneth
Limou, Sophie
Lin, Kuan-Hung
Linley, Laurie
Liu, Hongjie
Liu, Lin
Liu, Cindy
Llibre, Josep
Lo, Janet
Lo, Nathan
Loiseau, Claire
Longenecker, Chris
Low, Hui Zhi
Lu, Wuxun
Lu, Lydia
Lucera, Mark
Lundgren, Louise
Lutgen, Victoria
Luz, Paula
Ma, Qing
Mabileau, Guillaume
Macatangay, Bernard
Mackelprang, Romel
Maeda, Kenji
Makinson, Alain
Maman, David
Manel, Nicolas
Mangal, Tara
Manganaro, Lara
Mann, Marita
Manucci, Jordyn
Manuzak, Jennifer
Marinaro, Letizia
Maroa, Jenniffer
Marra, Christina
Martin, Alyssa
Martin, Michael
Martin, Jeffrey
Martin, Philip
Martin-Blondel, Guillaume
Martinez, David
Martinez-Pourcher, Valérie
Martin-Gayo, Enrique
Martinson, Jeremy
Marzel, Alex
Marzolini, Catia
Masciotra, Silvina
Massanella, Marta
Masur, Jack
Matoba, Nobuyuki
Matsuda, Kenta
May, Margaret
McGovern, Mark
McGowan, Ian
McKnight, Aine
Meditz, Amie
Medline, Alexandra
Mehta, Shruti
Mehta, Sanjay
Meissner, Eric
Menager, Mickael
Meya, David

Micci, Luca
Milanini, Benedetta
Miller, William
Milligan, Caitlin
Milligan, Michael
Mills, Edward
Mirani, Gayatri
Mirochnick, Mark
Mitchell, Brooks
Mocroft, Amanda
Moesker, Bastiaan
Molsberry, Samantha
Moore, David
Morgand, Marion
Mori, Masahiko
Mosepele, Mosepele
Moss, Darren
Mourez, Thomas
Moyo, Sikhulile
Muganzi, Davis
Mugwanya, Kenneth
Mujugira, Andrew
Mukherjee, Pranab
Murphy, Gary
Murray, Lyle
Murrell, Ben
Musselwhite, Laura
Muthu, Shankar Esaki
Mutimura, Eugene
Mwimanzi, Philip
Myer, Landon
Mylvaganam, Geetha
Naidoo, Anushka
Nakanjako, Damalie
NALINTYA, ELIZABETH
Namakula, Rhoda
Narla, Venkata
Nasrullah, Muazzam
Ndawinz, Jacques
Ndhlovu, Zaza
Negredo, Eugenia
Nel, Annalene
Nelson, Julie
Nevot, Maria
Newman, Laura
Ngoupo, Paul Alain
Nichols, Sharon
Nichols, Brooke
Nicol, Mark
Nijhuis, Monique
Njuguna, Irene
Nkengasong, John
Noel, Nicolas
Novitsky, Vladimir
Oberle, Corinna
O'Brien, Meagan
Olagunju, Adeniyi
Olesen, Rikke
Olivieri, Kevin
Olson, Ashley
Onyekwena, Obinna
Orem, Jackson
Orikiiriza, Judy
Orrell, Catherine
Osei-Kuffour, Edmund
Oster, Alexandra
Overbaugh, Julie
Overton, Edgar
Palk, Laurence
Palladino, Claudia
Palmer, Sarah
Palmer, Clovis
Panayidou, Klea
Pandrea, Ivona
Panichsillapakit, Theppharit
Panigrahi, Soumya
Papasavvas, Emmanouil
Paraskevis, Dimitrios
Parikh, Urvi
Passo, Marcel Tongo
Pasternak, Alexander
Pate, Kelly
Patel, Pragna
Patel, Eshan
Paul, Biswajit
Payne, Brendan
Payne, Helen
Paz-Bailey, Gabriela
Pei, Luxin
Penrose, Kerri
Pérez-Santiago, Josué
Permar, Sallie
Pernas, Maria
Perumalswami, Ponni
Peterson, Christopher
Petrovas, Constantinos
Phillips, Tamsin
Pierre, Samuel
Piggott, Damani
Pilcher, Christopher
Pinnetti, Carmela
Pino, Maria
Pinto Cardoso, Sandra
Pinzone, Marilia
Pitts, Robert
Pohlmeyer, Christopher
Poizot-Martin, Isabelle
Policicchio, Benjamin
Post, Jeffrey
Potempa, Marc
Poulsen, Susanne
Powis, Kathleen
Prasad, Ramakrishna
Prendergast, Andrew
Price, Alison
Puligujja, Pavan
Purdy, Julia
Purswani, Murli
Pyndiah, Nitisha
Quenneville, Simon
Quinn, Thomas
Rachlis, Beth
Radzio, Jessica
Ragonnet-Cronin, Manon
Ragupathy, Viswanath
Rahimy, Elham
Raifman, Julia
Rainho, Jennifer
Rainwater-Lovett, Kaitlin
Ramos, Eric
Ramteke, Sarah
Ravimohan, Shruthi
Rawizza, Holly
Razeghi, Sanam
Re, Vincent Lo
Reardon, Brian
Rebeiro, Peter
Redd, Andrew
Reed, Jason
Rees, Helen
Reh, Lucia
Reniers, Georges
Reszka-Blanco, Natalia
Rey, David
Reynolds, Steven
Rhein, Joshua
Richards, Elizabeth
Richards, Maureen
Rivero-Juarez, Antonio
Riyaten, Prakit
Roan, Nadia
Robbins, Danielle
Roberts, Allen
Roberts, Sarah
Robertson, Kevin
Rocafort, Muntsa
Rodriguez-Hart, Cristina
Rodriguez-Mora, Sara
Rohr, Julia
Rolland, Morgane
Romas, Laura
Rosen, Sydney
Rosen, Elias
Rosenberg, Eli
Rower, Joseph
Roxby, Alison
Ruelas, Debbie
Rugwizangoga, Eugene
Ruiz-Cruz, Matilde
Ryom, Lene
Saafir-Callaway, Brittani
Saberi, Sara
Sabharwal, Charulata
Sacktor, Ned
Sagar, Manish
Saïdi, Hela
Sainz, Talía
Sakai, Keiko
Sakoda, Marissa
Salazar-Austin, Nicole
Salazar-Vizcaya, Luisa
Salgado, Maria
Salinas, Jorge
Salvadori, Nicolas
Samarawickrama, Amanda
Samji, Hasina
Sanders, Rogier
Sanders, Eduard
Sandkovsky, Uriel
Santelli, John
Saravanan, Shanmugam
Sardo, Luca
Sauter, Daniel
Saylor, Deanna
Scagnolari, Carolina
Scarsi, Kimberly
Schackman, Bruce
Schechter, Melissa
Schenkwein, Diana
Schmidt, Axel
Schneider, John
Schuetz, Alexandra
Schwartz, Sheree
Scott, Hyman
Scott-Algara, Daniel
Scriven, James
Scully, Eileen
Sebastian, Thresia
Seddiki, Nabila
Seifert, Sharon
Seifert, David
Serghides, Lena
Serrano-Villar, Sergio
Shah, Monica
Shah, N. Sarita
Shah, Maunank
Shan, Liang
Sharma, Anjali
Sharma, Amit
Shaw, Souradet
Shearer, William
Sherman, Kenneth
Shiboski, Caroline
Shih, Ivy
Shilaih, Mohaned
Shirazi, Talia
Shivakoti, Rupak
Siddiqi, Azfar-e-Alam
Sidharthan, Sreetha
Silverman, Rachel
Silvestri, Guido
Simmons, Ruth
Simonetti, Francesco
Singh, Kumud
Sinha, Arjun
Sionean, Catlainn
Slyker, Jennifer
Smit, Colette
Smith, Bryan
Smith, Adrian
Smith, Jennifer
Smith, Robert
So-Armah, Kaku
Sodora, Donald
Solomon, Sunil
Soulie, Cathia
Soumana, Djadé
Spinner, Christoph
Spragg, Chelsea
Spudich, Serena
Srinivasa, Suman
Sripan, Patumrat
Stankov, Metodi
Stary, Georg
Stephenson, Kathryn
Stiegeler, Emanuel
Strbo, Natasa
Streeck, Hendrik
Su, John
Suarez, Guadalupe
Sudfeld, Christopher
Svicher, Valentina
Swain, Carol-Ann
Swartz, Talia
Takuva, Simbarashe
Tan, Darrell
Tang, Yuyang
Tang, Weiming
Tanser, Frank
Technau, Karl-Günter
Teodorof, Carmen
Theys, Kristof

Thiebaut, Rodolphe
Thirumurthy, Harsha
Thomas, Aurielle
Thompson, Corbin
Thomson, Kerry
Tinago, Willard
Todd, Catherine
Tomescu, Costin
Torian, Lucia
Townsend, Kerry
Toyoda, Mako
Trevillyan, Janine
Triant, Virginia
Trkola, Alexandra
Truong, Hong-Ha
Tsao, Li-Chung
Tsibris, Athe
Tucker, Katie
Tuyishime, Marina
Tzarnas, Stephanie
Ueno, Takamasa
Uprety, Priyanka
Utay, Netanya
Valcour, Victor
Valente, Susana
Valere, Kimyata
Vallari, Ana
Van Cutsem, Gilles
van der Heijden, Yuri
van der Sluis, Renee
van der Straten, Ariane
Van Zoest, Rosan
Vanhommerig, Joost
Vanobberghen, Fiona
Var, Susanna
Vardhanabhuti, Saran
Vazquez, Homero
Vera, Jaime
Verheyen, Jens
Vernazza, Pietro
Vigano, Selena
Villegas, Guillermo
Vinikoor, Michael
Vita, Serena
Vitomirov, Andrej
Vojtech, Lucia
Vollbrecht, Thomas
von Stockenstrom, Susanne
Wahl, Angela
Wakefield, Steven
Walker, Joshua
Walker, Naomi
Walker-Sperling, Victoria
Wang, Zhengyan
Wang, Yuge
Wanga, Valentine
Watters, Sarah
Wechsberg, Wendee
Weis, Julie
Welte, Alex
Wertheim, Joel
Westheimer, Emily
White, Cory
White, Ellen
Wiboonchutikul, Surasak
Wilkin, Timothy
Wilson, David
Wilson, Kate
Wilson, Eleanor
Wittkopp, Cristina
Wohlfeiler, Michael
Wood, Lianna
Wright, Patrick
Wu, Hsiu
Wu, Julia
Yang, Lifei
Yanik, Elizabeth
Yebra, Gonzalo
Yek, Christina
Yi, Guohua
Ying, Roger
Yoh, Sunnie
Yong, Michelle
Yoshinaga, Noriyoshi
Yucha, Robert
Zahnd, Cindy
Zakhour, Ramia
Zash, Rebecca
Zayyad, Zaina
Zeh, Clement
Zentner, Isaac
Zerbato, Jennifer
Zerbe, Allison
Zheng, Yonghui
Zulu, Fatima

AUTHOR INDEX

Bold numbers indicate a presenting author role for that abstract.

– A –

Abassi, Mahsa; **454**
Abayisenga, Gloriose; 1087, 1087
Abbara, Suhny; 136, 138
Abbott Klafter, Jesse; **1005**
Abd-Elmoniem, Khaled; 928
Abdel-Hameed, Enass; **698**
Abdel-Mohsen, Mohamed; **386**
Abdool Karim, Quarraisha; 984
Abdool Karim, Salim S.; 984, 987
Abdullah, Kameelah L.; 929
Abecasis, Ana B.; 610
Aberg, Judith; 90
Abgrall, Sophie; 727, 727
Abildgaard, Julie; 803
Ablanedo-Terrazas, Yuria; 848
Aboud, Michael; 550
Aboud, Said; 606
Abraham, Alison G.; **797**
Abraham, Bisrat; 1001
Abrahantes, Yeissel; 338
Abrams, Elaine J.; 864, 864, 873, 880, 888, 914
Abramson, Jeremy; 718
Abuku, Ekii A.; 817
Abutarif, Malaz; 509
Abzug, Mark; 917
Abzug, Mark J.; 944
Achan, Jane; 513, 617
Achenbach, Chad; 726, 726
Achhra, Amit C.; **315**
Achim, Cristian L.; 436, 464
Achim, Cristian; 481
Achim, Cristian L.; 499
Ackerman, Margaret E.; **64**
Ackerman, Peter; 151LB
Acosta, Edward A.; 517
Adams, Joella W.; **890**
Adebajo, Sylvia; 1063, 1063
Adejuyigbe, Ebunoluwa; 533, 533
Adeola, Juliet; 1015
Adeyemi, Oluwatoyin M.; 319, **486**
Adhiambo, Judy; 911
Adland, Emily; 921
Adler, Michelle; 875
Admani, Bashir; 889
Adonis, Lungiswa; 823
Aga, Evgenia; 110LB
Agaba, Patricia; **1075**
Agan, Brian K.; **565**, 847
Agbaji, Oche; 1075
Agins, Bruce D.; 1002
Agolory, Simon; 155, 938
Agsalda-Garcia, Melissa A.; **480**
Agudelo-Hernandez, Arcadio; 389LB
Agüero, Fernando H.; **640**
Aguilera-Sandoval, Christian-Raul; 365
Aguirre, Alfredo; 860, 860
Agwu, Allison; 1065
Ahlgren, Erika; **470**
Ahmed, Aabid; 278
Ahmed, Hayat; 110LB
Ahonkhai, Aimalohi A.; **1015**
Ahoua, Laurence; 873
Ahrenstorf, Gerrit; 282, **297**
Ait-Khaled, Mounir; 609
Ajaykumar, Abhinav; **881**
Ajibola, Gbolahan; 870
Akanmu, Alani S.; 574
Akanmu, Alani Sulaimon; 118
Akanmu, Sulaimon; 940
Akbar, Ali; 693
Ake, Julie; 459, **764**
Akinwumi, Segun M.; 471
Akiyama, Hisashi; **188**, **188**, 222
Akleh, Rana; 43
Al-Hadab, Ali; 838, 838
Al-Harthi, Lena; **478**, 507, 508
Al-Mubarak, Reem; 309
Alam, Muntasir; **589**
Alam, Rafeul; 312
Albert, Arianne; 881
Albert, Jan; 229
Albert, Matthew L.; 681
Albrecht, Mary; 307
Alcaide, Maria L.; 273
Alcami, Jose; 196
Aldamiz-Echevarria, Teresa; 682
Alegre, Fernando; 500
Alejos, Belen; 918
Aleman, Karen; 87
Alemán, Yoan; 338
Alessandri-Gradt, Elodie; 257, 257
Alfaro, Raul; 520
Alger, Jeffrey; 490
Alimenti, Ariane; 881
Alinejad-Rokny, Hamid; 363
Aliyu, Muktar H.; **558**
Allana, Salim; 92
Alland, David; **91**, 824
Allavena, Clotilde; 575
Allen, Monique; 658, 668
Allen, Susan; 54LB, 364, 1044
Almirall, Daniel; **7**
Almond, Steve; 550
Alsina, Merçe; 845
Alter, Galit; **1**, 339
Alteri, Claudia; 702
Altfeld, Marcus; 307
Althoff, Keri N.; **726**, 748, 580, 638, **726**, 748, 749LB, 786, **1053**
Aluzimbi, George; **1037**
Alva Hernández, Selma N.; **264**, 265
Alvarado-de la Barrera, Claudia; 848
Alvarez, Angeles; **735**
Alvarez, David; 357
Alvarez, Hortensia; 553
Alvarez-Fernandez, Carmen; 354
Aly, Dario; 873
Amadori, Celine; 540
Amanyire, Gideon; 1071
Amara, Alieu; 533, 533
Amara, Rama R.; 370
Ambrose, Zandrea; 188, 188
Ambrozak, David; 49, 394
Amico, K. Rivet; 970
Amico, Rivet; **977**, 978LB
Amin, Janaki; 779, 779
Ammassari, Adriana; 63
Ammerlaan, Heidi; 659
Amos, Joshua; 903
Amraoui, Sonia; 329
An, Qian; 100, 1043
Anand, Sean S.; 842
Ananworanich, Jintanat; 47, 48, 272, 438, 473, 480, 841
Anastos, Kathryn; 780, 294, 516, 775, 780, 792
Ances, Beau; 60, 447, 488
Andersen, Åse; 325
Anderson, Albert M.; 440
Anderson, Bridget J.; 599, 1002
Anderson, Christy; 240, 375
Anderson, Christy M.; 1021, 1022
Anderson, Elizabeth M.; **420**
Anderson, Jane; 332, 560
Anderson, Jeffrey; 523
Anderson, Matt S.; 521
Anderson, Peter L.; 81, 83, 514, 525, 526, 970, 977, 978LB, 992LB
Andersson, Lars-Magnus; 470
Ando, Dale; 434
Andrade, Bruno; 302, 268, 302, 311
Andrade, Viviane; **190**
Andrade-Villanueva, Jaime; 143LB
Andreoni, Massimo; 611
Andreotti, Mauro; **879**
Andres, Cristina; 354
Andrés, Cristina; 587
Andreu, Antonio Luis; 196
Andrews, Robert K.; 736
Anesten, Birgitta; **59**
Angarone, Michael; 649, 649
Angelico, Mario; 699
Angelidou, Konstantia; 36, 924
Angelis, Kostantinos; 229
Angerami, Matias T.; 821
Anglaret, Xavier; 115LB
Antela, Antonio; 553
Anthony, Donald; 684
Antinori, Andrea; 63, 442, 562, 611
Anton, Peter A.; 289
Anton, Peter; 994
Antonelli, Guido; 296
Anywaine, Zacchaeus; 94
Anzala, Omu; 1044
Aouizerat, Bradley; 294, 516
Apetrei, Cristian; 268, 406, 965
Apondi, Rose; **1039**
Apornpong, Tanakorn; 703
Apostolova, Nadezda; 500
Appelberg, Sofia; **183**
Applebaum, Allison; 446
Aquilante, Christina; 518
Aragri, Marianna; 702
Arainga, Mariluz; 543
Araínga, Mariluz; 529
Arbess, Gordon; 448, 465, 467
Archary, Moherndran; 36, **939**
Archin, Nancie; 372
Arenas-Pinto, Alejandro; **457**
Arend, S.; 659
Arends, Joop E.; 659, 669, 674
Aris, Eric; 606
Ariyoshi, Koya; 275, 276
Armenia, Daniele; **611**
Armon, Carl; 747, 312, 747, 997
Armstrong, Adam; 565
Armstrong, Wendy; 1068
Arnold, Vincent; 52
Arpadi, Stephen M.; 873, 930, **932**
Arribas, Jose R; 766, 795
Arrildt, Kathryn; 221
Arthur, Jane F.; 736
Arts, Eric J.; 215
Arumugam, Karthik; 213
Asahchop, Eugene L.; **471**
Asari, Villeshni; 984
Ásbjörnsdóttir, Kristjana H.; 861, 861, 884
Aschheim, Josh; 141
Ashengo, Tigistu; 1086, 1087, 1086, 1087
Ashton, Laura; 309
Asiimwe, Anita; 865, 865
Asiimwe, Stephen; 24
Asmelash, Aida; 711
Asmuth, David; 778, 267, 270, 310, 313, 547, 548, 778
Assane, Mariamo; 615
Assoumou, Lambert; 564
Astrakhan, Alexander; 401
Asugeni, Lester; 1089, 1089
Atkinson, Claire; 884
Attia, Alain; 807
Attia, Engi F.; **800**
Attwa, Fr. Mena; 800
Aubert, Martine; 400
Aubert, Vincent; 244, 245
Audigé, Annette; 207
Augenbraun, Michael; 639, 676
Auld, Andrew F.; **155**
Auld, Andrew; 938
Aurpibul, Linda; 915, **956**

Auyeung, Kate; 117
Avelino-Silva, Vivian I.; **318**
Avettand-Fenoel, Véronique; 333, 334
Avihingsanon, Anchalee; 511, **703**, 795
Avila-Rios, Santiago; **242**, 601, **607**, 848
Avornu, Ama; 667
Aweeka, Francesca T.; **513**
Ayangma, Liliane; 782, 782
Aydin, Cihan; 693
Ayieko, James; 740
Ayinde, Diana; 206
Ayodele, Adebisi O.; 666
Ayres, Lauren; 652
Azih, Charles; 155
Azzoni, Livio; 376

– B –

Ba, Selly; 541, 588, 614
Babigumira, Joseph; 712
Babiker, Abdel; 35, 111LB, 766
Babudieri, Sergio; 699
Babusis, Darius; 530
Bacchetti, Peter; 209, 294, 382, 428LB, 516, 887
Back, David; 85LB, 86LB, 531, 532, 533, 531, 532, 533, 964
Bade, Aditya N.; **504**
Bader, Joëlle; **336**
Badia, Roger; 204, 205
Badje, Anani; 115LB
Bae, Helen; 421LB
Baeten, Jared; **24**, 1111, 290, 969, 976, 980, 981, 983, 988, 989, 1106, 1111
Bagenda, Leonard; 119
Baggaley, Rachel C.; **177**
Bahr, Nathan C.; 836, **826**, 836
Bailer, Robert; 346
Bailey, Justin R.; 685
Baker, David; 733
Baker, Jason V.; 772
Baker, Laurie; **447**, 488
Bakken Kran, Anne-Marte; 602
Bakoyannis, Giorgos; 1072
Balabanian, Karl; 723
Balagopal, Ashwin; 778, **179**, **313**, 380, 778
Balaji, Alexandra B.; 1041, **1058**
Balakrishnan, Pachamuthu; 641, 704
Balamane, Maya; 597
Balamurugan, Arumugam; 365
Balestra, Pietro; 63
Balestre, Eric; **576**
Balkundi, Shantanu; 528
Balkus, Jennifer E.; **1033**
Ball, Terry B.; 287
Ballana, Ester; **204**, **205**
Baltussen, Rob; 159
Balzer, Laura; 740
Bañares, Rafael; 657
Banchereau, Jacques; 206, 353
Bandera, Alessandra; **466**
Banga, Riddhima; 422
Bangsberg, David R.; 295, 317, 556, 559, 722, 899, 976
Bangsberg, David; 988
Bangsberg, David R.; 1080
Banigbe, Bolanle; 1015
Bansal, Anju; 364
Baouchi-Mokrane, Fafa; 81, 518
Bar, Katharine J.; **349**
Baral, Stefan; **73**, 1063, 1063
Barash, Elizabeth A.; 1066, 1093
Barcena, Rafael; 640
Bargallo, Manel E.; 960
Baribwira, Cyprien; 865, 865
Barin, Burc; 799
Barin, Francis; 345
Barlow-Mosha, Linda; **36**, 939
Barnabas, Ruanne V.; 1111, 1106, 1111, 1112
Barnable, Patrick; 967, 968
Barnes, Lisa; 486
Barnes, Tiffany L.; 108
Barnett, Louise; 900
Barnighausen, Till; 1110, 157, 159, 896, 991LB, 1102, 1110
Baron, Deborah; 26LB
Barouch, Dan H.; **67**, 430
Bartha, Istvan; 293
Bartha, István; **291**
Barton, Kirston M.; 109
Basco, Brian; **488**
Basilissi, Matteo; **705**
Bassett, Ingrid V.; **93**, 1015
Bassett, Jean; 895
Batavia, Ashita; 156
Batavia, Ashita S.; **546**
Batisse, Julien; 193
Batista, Ana Paula; 318
Battegay, Manuel; 531, 531, 675
Battisti, Arianna; 702
Baudy-Floc'h, Michele; 213
Bauer, Jan; 814
Baugh, B; 893
Baugher, Amy R.; **1057**
Baughman, Andrew L.; 155, 938
Baumgarten, Axel; 646, 646, 671
Bavaro, Mary; 847
Bavinton, Benjamin R.; 1019LB
Baxi, Sanjiv M.; **516**, **792**
Baxter, Cheryl; 984
Baxter, Joanne; 798
Bazile, Junior; 721
Beagle, Steve; 1003, 1018
Beauchamp, Gheetha; 29, 1095, 1100
Beauparlant, David; 218
Bebawy, Sally; 741
Bebu, Ionut; 565
Beceiro, Jose; 942
Beck, Graham A.; 753
Becker, James T.; **463**, 489, 490, 493, **494**, 506
Becker, Marissa; 1054
Bedi, Keabetwe; 870
Bedimo, Roger; 728, 141, 728
Bedison, Margaret A.; 379, 379, 912
Bednar, Maria M.; **112LB**, **221**
Beekmann, Susan E.; 1083
Beer, Linda; 974, 1057
Beerenwinkel, Niko; 255, 255
Begley, Rebecca; 951
Behrens, Georg; 395
Beisel, Claudia; **341**
Bekele, Tsegaye; 448, 465
Bekker, Linda-Gail; 864, 514, 864, **978LB**, 1080
Bélanger, Maud; 534, 534
Belaunzarán-Zamudio, Pablo F.; 308
Beliakova-Bethell, Nadejda; 408, 409
Belisle, John; 309
Belissa, Emilie; 891
Belknap, Robert; **827LB**
Bell, Cynthia; 922
Bell, Matthew T.; 666
Bellocchi, MariaConcetta; 702
Belloso, Waldo; 779, 779
Ben Farhat, Jihane; 555, 1014, 1090
Benaboud, Sihem; 512, 949
Benarous, Richard; **540**
Benator, Debra; 824
Benchikh, Amine; 891
Bendavid, Eran; 157, 160, **832**, **1109**, 1121
Bendayan, Reina; 534, 534
Bender Ignacio, Rachel A.; **27**
Benet, Susana; 283
Benfield, Thomas; 316
Benjamins, Laura; 922
Benki-Nugent, Sarah; 911
Benko, Erika; 271
Bennett, Amy; 238, 1093
Bennett, David; 486
Bennett, Kara; 870
Bennett, Sean R.; 951, 952, **953**
Benson, Constance A.; 828LB
Berendes, Sima; 567
Berenguer, Juan; **657**, 682
Berg, Michael G.; **257**, **257**
Berger, Jeffrey S.; 284
Berhanu, Rebecca H.; 571, **829**, 1120
Berkhout, Ben; 384, 383, 384, 540
Bermejo, Mercedes; 196
Bernard, Cora; **1121**
Bernard, Daphne C.; 546
Bernard, Nicole F.; 277
Bernardino, Jose I; **766**, 918
Bernlochner, Isabell; 730
Bertagnolio, Silvia; 595
Bertisch, Barbara; 150
Bertz, Richard; 509
Berzins, Baiba; 451, 769LB
Best, Brookie M.; 436, **892**, 894
Beste, Jason A.; 721
Betsem, Edouard; 237
Beuscart, Aurélie; 139
Bevans, Margaret; 87
Bezemer, Daniela; 252, 1007, 1048, 1117
Bhagani, Sanjay R.; 798
Bhakta, Nirav; 759
Bharaj, Preeti; 356
Bhardwaj, Nina; 284, 323
Bhatia, Nisha; 439
Bhattacharya, Debika; **15**, 656, 672
Bhatti, Laveeza; 147
Bhaumik, Siddhartha; 898
Bhosale, Ramesh; 710
Bibby, David F.; 332
Bibollet-Ruche, Frederic; 44
Bicego, George; 155, 938, 1013
Bicer, Ceyhun; 551
Bich, Dang T.; 843
Bichoupan, Kian; **149**, 648, 647, 648
Bigger, Elizabeth; 718
Bigoloni, Alba; 443, 773
Bijker, Rimke; **557**
Bility, Moses T.; **677**
Binda, Kelebogile; 871
Binns, Jacquelyn; 449
Binns-Roemer, Elizabeth; 197
Birhanu, Sehin; 631
Birse, Kenzie; 269
Birx, Ambassador Deborah L.; **96**
Bishop, Courtney; 477
Bisson, Gregory P.; 810
Bitnun, Ari; 881
Black, Andrew; 829
Blackburn, Elizabeth; 784
Blanchard, James; 968
Blanche, Stéphane; 334, 867, 949
Blanco, José L.; **845**
Blanco, Julià; 260, 261, 331
Blanes, Marino; 640
Blankson, Joel; 427, 393, 427
Blankson, Joel N.; 623
Blas-García, Ana; 500
Blaschke, Terrence; **8**
Blashill, Aaron; 804
Blattner, William; 1063, 1063
Blatyta, Paula; 1010
Blevins, Meridith; 558, 762
Blick, Gary; 434
Bloch, Mark; 733
Blower, Sally; 1034, 1045
Bluemke, David; 756
Blum, Martha L.; 672
Blumberg, Emily; 799
Boasso, Adriano; 477
Bobrow, Emily A.; **865**, **865**
Boccara, Franck; 138
Bock, Naomi; 1013
Bocquet, Laurence; 232
Boeckh, Michael; 884
Boender, Tamara Sonia; **118**, 574
Boeree, Martin J.; **95LB**
Boesecke, Christoph; **670**, 678, 679
Boettiger, David C.; **915**
Boffito, Marta; **80**, 86LB
Bogart, Laura M.; 93
Boggavarapu, Sahithi; 898
Bohjanen, Paul; 834, 815, 834
Bohlius, Julia; 724, 724
Bohn, Patrick; 363
Boix, Jaume; 964
Bokatzien, Sam; 309
Bokhart, Mark T.; 535, 535
Bolaji, Oluseye; 533, 533
Bolan, Robert; 254, 254, 797
Bolivar, Hector; 273
Bolon, Dan; 216
Bolouri, Hamid; **13**
Bolton, Diane L.; **50**
Bolton, Diane; 166
Bolton Moore, Carolyn; 808
Boltz, Valerie F.; **593**, **593**
Bonczkowski, Pawel; **424**
Bonfanti, Paolo; **765**
Boni, Jurg; 253
Böni, Jürg; 244, 245, 336
Bonjoch, Anna; 767
Bonnard, Damien; 540
Bonnet, Fabrice; 727, 727
Bonora, Stefano; 487, 791
Bont, Jan D.; 1038

Boobalan, Jayaseelan; 704
Boonchawalit, Samatchaya; 590
Booth, John; 794
Bor, Jacob; **1110**, **1110**
Borderi, Marco; 773
Borgdorff, Martinus W.; 625, 624, 625
Borges, Álvaro H.; **761**
Borisov, Andrey; 827LB
Boritz, Eli; 394
Borkowsky, Bill; 278, 905
Bornfleth, Lorelei; 226, 672
Borrow, Persephone; 44, 54LB, 169
Bosch, Jordi; 845
Bosch, Ronald; 110LB, 307, 763
Bosinger, Steven; 326, 370
Bosire, Rose; 1035
Boska, Michael; 504
Bosque, Alberto; 424
Boswell, Kristin; 167
Boswell, Stephen; 1065
Botes, Mariette E.; 118
Bouazza, Naïm; 863, 863, 949
Boucher, Charles; 229, 1105
Bouchez, Sabelline; 1009
Boue, Francois; 723
Boufassa, Faroudy; 52, 333
Bouhenia, Malika; 555, 1014
Boulle, Andrew; 920
Boulton, David W.; 509, 523
Boulware, David R.; 834, 835, 836, 838, 454, 573, 815, 826, 834, 835, 836, 838
Boum, Yap; 317, 556, 899, 976
Bourdery, Laure; 819
Bourgeois-Moine, Agnes; 891
Bourguignon, Lilly; 210
Bouvier, Magali; 232
Bouvin-Pley, Mélanie; 345
Bove, Joanna M.; **1092**
Bowles, Kristina; 1058
Bowman, Natalie M.; 439, 440, **445**
Bowonwatanuwong, Chureeratana; 511
Boyd, Anders C.; 671, **706**
Boyd, David F.; **280**
Boyd, Mark A.; **779**, **779**
Boyee, Dorica; 1086, 1086
Boylan, Ross; 294
Boyle, Jeffrey; 281
Bradaric, Christian; 730
Bradley, Heather; **1064**
Brady, Jennifer; 774
Brady, Kathleen A.; **1062**
Brady, Kathleen; 890
Brady, Kathleen A.; **1028**, **1062**
Braibant, Martine; 345
Braithwaite, R. Scott; 1072
Braitstein, Paula; 1072, 1073
Branch, Andrea D.; 149, 648
Branch, Andrea; 647
Branch, Andrea D.; 648
Brand, Hilmarie; 622, 622
Brandeau, Margaret L.; 1121
Brandenberg, Oliver; 39
Branson, Bernard M.; 29, 621, 1095, 1100, 1113
Branton, William G.; 471
Bras, Marlène; 285
Brasacchio, Caterina; 765
Brassard, Pierre; 534, 534
Brassat, David; 814
Brau, Norbert; 687
Braunlin, Megan; 1113
Braunstein, Sarah L.; 99, 729, **1001**, 1069
Bravo, Isabel; 260, 261
Breen, Delisha; 645, 645
Breen, Michael S.; 408
Brejda, John; 521
Brenchley, Jason M.; 168
Brennan, Alana T.; 781, 781
Brennan, Catherine; 257, 234, 257
Brennan, Clare; 550
Brenner, Bluma; **251**, 591
Brew, Bruce J.; 59
Brew, Bruce; 437
Brew, Bruce J.; **441**
Brew, Bruce; **505**
Brezar, Vedran; 206, **353**
Briggs, Melissa A.; **938**
Brinkman, Kees; 659, 674
Brinkmann, Christel R.; 405
Brinson, Cynthia C.; 554LB
Briz, Verónica; 950
Brocca-Cofano, Egidio; 406, **965**
Brockman, Mark A.; 227
Brockman, Mark; 228, 536
Brodsky, Allison; 658, 668
Broliden, Kristina; 287
Bronowicki, Jean-Pierre; 687
Brooks, John T.; 747, 747, 749LB, 772, 997, 1027
Brooks, Katherine C.; **597**
Brophy, Jason; 881
Brouillette, Marie-Josée; **469**
Brown, Alison; 154
Brown, Biobele; 940
Brown, Elizabeth R.; 979
Brown, Eric; 846
Brown, K; 893
Brown, Kevin; 538
Brown, Robert S.; **691**
Brown, Sheldon; 728, 728
Brown, Todd T.; 140, 489, 769LB, 783, **786**, **787**
Browne, Sara; **828LB**, 926, 929
Browning, Renee; 31LB
Broz, Dita; 998
Bruckman, Rachel S.; 387, 410
Brumme, Chanson J.; 291, **592**, 697
Brumme, Zabrina L.; 227, 228, 536
Brummel, Sean; 924
Bruneau, Julie; 277
Brunetta, Jason; 448, 465, 467
Brusamento, Serena; 873
Brust, James C.; 92
Bryant, Kendall; 1050
Buacharern, Marc; 82
Buchacz, Kate; 747, 747, **997**, **1095**, 1100
Buchbinder, Susan P.; **3**, 25, 970, 1017
Bucher, Heiner C.; **720**
Buckheit, Karen W.; 510
Buckheit, Robert; 510
Buckler-White, Alicia; 503
Buckner, Clarisa M.; 340
Budoff, Matthew J.; 748, 748
Buechler, Matthew B.; **946**
Bui, John; 389LB
Bukusi, Elizabeth; 24, 989, 1072
Bull, Marta E.; **107**
Bullen, C Korin; 419
Bullen, C. Korin; 427, 427
Bullock, Brandon; 416
Bulya, Nulu; 1106
Bulya Semiyaga, Nulu; 969
Bumpus, Namandje; 428LB
Bumpus, Namandjé; 436
Buño, Antonio; 766
Burbelo, Peter; 302, 302
Burch, Lisa S.; **560**
Burchard, Gerd D.; 849
Burchell, Ann N.; 448, 465, 467
Burdick, Ryan C.; 45
Burdo, Tricia; 317
Burdo, Tricia H.; 753, 899
Burgener, Adam; **269**, 287
Burgener, Adam D.; 289
Burger, David; 892
Burgers, Wendy A.; 231
Burgey, Christopher; 449
Burgos, Joaquin; **714**
Burke, Leah A.; 644, 644
Burke-Miller, Jane; 1050
Burkholder, Greer; 804, 1004
Burstein, Roy; 584
Busch, Heiner; 646, 646
Busch, Michael; 258, 626, 258, 626
Buseyne, Florence; **237**, **334**
Bush, Tim; 713
Bush, William; 460
Bushman, Frederic D.; **12**
Bushman, Lane; 81
Bushman, Lane R.; 83, 525
Bushman, Lane; 526
Buskin, Susan E.; **238**, 1066, 1093
Bussmann, Hermann; 630, **990**
Busuulwa, Monday; 577
Butler, Karina M.; **38LB**
Butler, Katherine; 862
Butler, Laurie; 801
Butt, Adeel A.; 746, **642**, **643**, 746, 1049
Butterton, Joan; 521
Butterton, Joan R.; 522
Buus, Soren; 362
Buzaalirwa, Lydia; 577
Buzhdygan, Tetyana P.; 61
Bvochora-Nsingo, Memory; 711
Bwakura Dangarembizi, Mutsa F.; **916**, 941
Bwana, Mwebesa Bosco; 1072
Byakika-Kibwika, Pauline; 85LB
Byakwaga, Helen; 317, **722**, 899
Byonanebye, Dathan; 740
Byron, Mary Margeret; 796

– C –

Caan, Matthan W.; 935
Cabanas, Joaquim; 610
Cabié, André; 1009
Cabrera, Cecilia; 331, **964**
Cacciotti, Giulia; 296
Cacopardo, Bruno; 776
Cagigi, Alberto; 947
Cahn, Pedro; 545
Cahn, Pedro E.; 580
Cai, Suqin; 696
Cain, Lauren E.; 837, 837
Calcagno, Andrea; **487**, 791
Calderon, Monica M.; **520**
Calenda, Giulia; 967, **968**
Callard, Robin; 35
Callebaut, Christian; 113LB, **530**
Calmy, Alexandra; 675, 761
Calvert, Clara; **583**
Calvez, Vincent; 564
Calvo, Katherine R.; 340
Camacho, Angela; 709
Camacho, Ricardo J.; 610
Camacho-Gonzalez, Andres F.; **944**
Cambou, Mary Catherine; 856
Cameron, Andrew; 380
Cameron, Mark; 292
Cameron, Paul; 281
Cameron, Paul U.; 388
Camós, Mireia; 923
Camp, Rob; 845
Campbell, Ellsworth; 241
Campbell, Grant R.; **387**, **410**
Campbell, Nottania K.; 218
Campbell, Thomas B.; 778
Campbell, Thomas; 313, 451, 567
Campbell, Thomas B.; 778
Campellone, Shalyn; 371
Campos, Noelie; 104LB
Canini, Laetitia; 148, 708LB
Canning, David; 1102
Cano, Carla E.; 575
Cantone, Joseph; 539
Cao, Huyen; 143LB
Capeau, Jacqueline; 138, 788
Capetti, Amedeo; 442
Capitant, Catherine; 23LB
Caplan, Margaret; 302, 302
Capoferri, Adam A.; 397
Capparelli, Edmund; 374, 894
Cappy, Pierre; **232**
Caramatti, Giada; 442
Carbarballo-Dieguez, Alex; 269
Carganico, Andreas; 671
Carlotti, Agnes; 723
Carlson, Jonathan M.; 364
Carmona, Sergio; 910
Carne, Simon; 618
Carnochan, Tara; 1054
Carpani, Giovanni; 705
Carr, Andrew; 958, 733, 958
Carrat, Fabrice; 701
Carrere, Nicolas; 274
Carrero, Ana; 682
Carroll, Courtney; 752, 755, 760
Carvalhal, Adriana; 448, 465, 467
Carvallo, Cristian; 430
Casadellà, Maria; 260, 261
Casado, Concepción; 347
Casalini, Catarina; 914
Casazza, Joseph; **49**, 394
Cashin, Kieran; **633**
Casrouge, Armanda; 681
Cassese, Salvatore; 730
Cassol, Edana; **498**
Casson-Crook, Martine; 455
Castagna, Antonella; 443, 562, 766, 773
Castel, Amanda D.; **660**, 665, 854
Castelli, Francesco; 655
Castells, Lluis; 640

Castilho, Jessica L.; **741**, **856**
Castillo-Mancilla, Jose R.; **83**, 525, 526
Castro, Pedro; 391, 391
Castronuovo, Daniela; 776
Catalina, María Vega; 657
Cauda, Roberto; 495
Cavassini, Matthias; 422
Cayla, Joan; 827LB
Cazabat, Michelle; 274
Ceccherini-Silberstein, Francesca; 594, 611, **699**
Celentano, David D.; 1016
Celesia, Benedetto M.; 776
Celum, Connie; 24, 1111, 622, 290, 292, 622
Celum, Connie L.; 623
Celum, Connie; 969, 976, 980, 981, 983, 988, 989, 1106, 1111
Cento, Valeria; 699
Cesar, Carina T.; **580**
Cespedes, Michelle; 90
Cha, Agnes; 647
Cha, Hyun A.; 666
Chabner, Bruce; 711, 718
Chadwick, Ellen G.; 374
Chadwick, Katy; 851
Chaganti, Joga; 441
Chahroudi, Ann; 944
Chaillon, Antoine; 219
Chaisson, Christine E.; 93
Chaisson, Richard E.; 822, 872, 907
Chaix, Marie Laure; 429
Chakraborty, Rana; 898, 944
Chakravorty, Soumitesh; 91
Chalamilla, Guerino; 606
Chalermpantmetagul, Suwalai; 831
Chamie, Gabriel; 1071, **1101**
Chan, Brian T.; **1059**
Chan, Chi N.; 426
Chan, Ellen; 769LB, 787
Chan, Jonathan; 385
Chan, Phillip; 437
Chancellor, Mitchell; 91
Chanda, Sumit; 40, 288
Chang, Christina; 428LB
Chang, Jee Yoon; 447
Chang, Joy; 615
Chang, Ming; 614, 617
Chang, Simon B.; 537
Chang, Sui-Yuan; **608**
Chang, Theresa; 211
Charalambous, Salome; 825
Charbit, Bruno; 285
Chariyalertsak, Suwat; 514
Charlebois, Edwin; 883, 887, 1056
Charlebois, Edwin D.; 1071
Charlebois, Edwin; 1101
Charles, Benedict; 156
Charpentier, Charlotte; 891
Charreau, Isabelle; 23LB
CHARTER Group, for the; 461
Charurat, Manhattan; 1063, 1063
Chasela, Charles S.; 33, 868, 886
Chavez, Leonard; 385, 386
Chavez, Pollyanna R.; **1100**
Chebani, Tony; 990
Chege, Duncan; 914
Chekuri, Sweta; 149
Chen, Benjamin K.; 220
Chen, Benjamin; 323
Chen, Cheng; 855
Chen, Chia-Yen; 503
Chen, De; 45
Chen, Diana Y.; 365
Chen, Fabian; 362
Chen, Huichao; 716, 844
Chen, Iris; **116**
Chen, Janet S.; 954
Chen, Jennifer Y.; 878
Chen, Jianbo; 45
Chen, Jing; 698
Chen, Michael; 827LB
Chen, Robert T.; 632LB
Chen, Xinhui; **526**
Chen, Yahui; 396
Chen, Yi-Ming A.; 235
Chen, Zhian; 358
Chene, Genevieve; 139, 766, 1051
Cheng, Andrew; 953
Cheng-Mayer, Cecilia; 344
Chenine, Agnes-Laurence; 170LB
Chentsova, Nelli; 1042
Cheret, Antoine; 575
Chernoff, Miriam; 917, 936
Chernoff, Miriam C.; 944
Chetchotisakd, Ploenchan; 795
Chetty, Terusha; 896
Cheung, Angela; 777
Chevigné, Andy; 213
Chew, Kara W.; **672**
Chi, Benjamin; 36
Chi, Benjamin H.; 808
Chiamwongpaet, Sithisat; 971
Chida, Natasha; 1108
Chidiac, Christian; 23LB
Chihana, Menard; 1046
Chihota, Violet; 823, 825
Chikata, Takayuki; 328
Chilima, Benson; 32, 153, 1079, 1090
Chilisa, Florence; 870
Chimbindi, Natsayi; 1110, 1110
Chimbwandira, Frank; 874
Chinappa, Tilagavathy; 830
Chingoli, Felix D.; 721
Chingondole, Christine; 874
Chinnery, Patrick F.; 785
Chinyanga, Yvonne; 876
Chioma, Stanley U.; 427, 427
Chipato, Tsungai; 31LB
Chirawatthanaphan, Patinun; 831
Chirenje, Z M.; 979, 982
Chittmittrapap, Salyavit; 703
Chiumya, Kondwani; 634
Chiumya, Regina; 885
Chkhartishvili, Nikoloz; 664
Chmiel, Joan S.; 747, 747
Chohan, Bhavna; 945, 946
Chohan, Bhavna H.; **1035**
Chohan, Vrasha; 906
Chokephaibulkit, Kulkanya; 943
Choko, Augustine T.; 634
Chomchey, Nitiya; 48, 272
Chomont, Nicolas; 48, 534, 354, 388, 413, 534
Chono, Hideto; 402
Choong, Ingrid; 708LB
Choopanya, Kachit; 635, 971, 986
Chow, Dominic C.; **754**, 796
Chow, Felicia C.; 475, **760**
Chowdhury, Ankita; **326**
Christ, Frauke; **198**
Christensen, Stefan; 646, 646
Christian, Parul; 567
Christopoulos, Katerina; 804, 1005
Chu, Yen-Lin; 387, 410
Chui, Celia K.; 592, 697
Chun, Tae Wook; 271, 340, 548
Chung, Michael; 866, 712, 800, 866, 1081
Chung, Raymond; 677
Chung, W-L Joanie; 842
Churchill, Duncan; 596
Churchill, Melissa J.; 633
Churchyard, Gavin; 823, 825
Chutanunta, Apichat; 788
Ciaffi, Laura; 782, 782, 793
Ciborowski, Pawel; 529
Ciccarelli, Nicoletta; 495
Cicconi, Paola; 303, 303, 636
Cieply, Lukasz; 662
Cifuentes, Celia; 709
Cihlar, Tomas; 108, 417
Cillo, Anthony R.; 379, 106, 379, 389LB, **398**
Cingolani, Antonella; 562, **636**
Cinque, Paola; 443
Cisse, Mohamed; 1077
Ciuffi, Angela; 191, 191
Claassen, Mark A.; 669
Claiborne, Daniel T.; 54LB
Clapham, Paul R.; 216
Clare, Laurel; 672
Claridge, Timothy; 497
Clark, Duncan A.; 332
Clark, Duncan; 596
Clark, Samuel; 583
Clark, Taane G.; 816LB
Clark, Tamara; 883, 887, 1056, 1071, 1101
Clarke, William; 98, 116, 629
Clement, Meredith E.; **750**, **750**
Clement, Tyler; 61
Clements, Janice; 416
Cleveland, Bradley; 348
Climent, Nuria; 354
Clotet, Bonaventura; 204, 205, 260, 261, 283, 331, 432, 553, 767, 964
Coates, Thomas J.; **74**, 629
Coburn, Brian J.; 1045
Cockerham, Leslie R.; **299LB**
Cocklin, Simon; 195, 212
Coetsee, Marla; 604
Coetzee, David; 314
Coetzer, Mia; 597
Coffin, John M.; **5**, 593, 105, 106, 420, 593
Coghill, Anna E.; **717**
Cohan, Deborah; 883, 887
Cohen, Craig R.; 980, 1072
Cohen, Karen; 559, **604**
Cohen, Mardge; 858, 294, 516, 770, 775
Cohen, Mardge H.; 792
Cohen, Mardge; 858, 1050
Cohen, Myron; 221
Cohen, Sophie; **935**
Cohen, Stephanie; 25, 620
Cohn, Silvia E.; **822**, 872
Cohn, Silvia; 907
Cohn, Susan; 85LB
Cohort Collaboration, PASER-TASER; 557
Coiras, Mayte; 196
Colan, Steven D.; 882
Colasanti, Jonathan; **1068**, **1074**
Colbers, Angela; 892
Colby, Donn J.; **841**
Cole, James; 477
Cole, Stephen R.; 578
Coleman, Sharon M.; 93
Colin, Andrew; 801
Coll, Josep; 260, 261, 964
Collado-Diaz, Victor; 735
Colley, Guillaume; 1055
Collins, Sarah; 662
Collins, Simon; 596
Collman, Ronald G.; 501, 502
Colvin, Lisa; 903
Compagnucci, Alexandra; 919
Compliment, Kara J.; 909
Compston, Juliet; 774
Conley, Lois; 713, 772
Connick, Elizabeth; 859, 426, 859
Connolly, John; 794
Connor, Matthew B.; 116
Connor, Matthew; 1100
Conyngham, S. Caitlin; 975
Cook, Adrian; 37, 927
Cook, Barbara; 522
Cook, Jennifer; 696
Cooke, Graham; 654
Coombs, Robert W.; 614, 617, 627, 710, 1006, 1070
Coomer, Charles; 593, 593
Cooney, Michael; 967
Cooper, Curtis; 152LB
Cooper, David A.; **19**, 779, 779
Cooper, Ellie; 1012
Cooper, Stewart; 708LB
Coovadia, Ashraf; 910, 932
Copas, Andrew; 1042
Cope, Anna B.; **1003**
Cope, Rebecca; 651, 651
Coppola, Nicola; 702
Corbett, Elizabeth L.; **634**
Cori, Anne; 249, **1048**
Corneil, Trevor; 1024
Cortes, Claudia P.; 833
Cory, David; 708LB
Cose, Stephen; 815
Costagliola, Dominique; 564, 579
Costantini, Alberto; 303, 303
Costarelli, Silvia; 655
Côté, Hélène; 306
Côté, Hélène C.; 881
Côté, Hélène; 901
Cotter, Aoife; 774
Cotton, Mark F.; 35, 912, 926, 929
Cotugno, Nicola; 947
Cournil, Amandine; **782**, **782**, **793**
Cowan, Frances M.; **135**
Cox, Andrea; 313, 673
Cox, Christopher; 743
Coyne, Matthew; 588
Cozzi-Lepri, Alessandro; **562**
Cozzi-Lepri, Alessandro D.; 636
Crabtree-Ramirez, Brenda; 833

Crampin, Amelia C.; 161, 816LB, 885, 1046
Crane, Heidi M.; 748, 748, 749LB, **804**, 1005
Cranmer, Lisa; 911
Cranston, Kevin; 613
Cranston, Ross; 269
Cranston, Ross D.; 994
Crauwels, HM; 893
Creighton, Jason; 455
Cremieux, Pierre; 1012
Cremin, Ide; 1107
Crescini, Melanie; 436, 444
Crespo, Manel; **414**, 553, 714
Cressey, Tim R.; 863, 863, **511**, 831, 894
Cristaudo, Antonio; 611
Crocker, Jonathan T.; 721
Crofoot, Gordon; 113LB, 795
Cronin, Jacqueline; 185
Crooks, Abigail; 840
Cropsey, Karen; 804
Cross, Gail B.; **1011**
Crothers, Kristina; 728, 728, 800
Crouch, Pierre-Cedric; 25
Crowe, Suzanne M.; 320
Crowell, Trevor A.; **48**
Crowley, Jeffrey; **129**
Crum-Cianflone, Nancy; **847**
Cuc, Ngo T.; 843
Cuffe, Robert; 550
Cui, Yanfang; 358
Cui, Zishan; 1023, 1024, 1025
Cummings, Jean-Saville; 52
Cummings, Vanessa; 116
Cummins, James E.; **966LB**
Cunningham, Coleen; 905
Cunyat, Francesc; 361
Curlin, Marcel E.; **635**
Curlin, Marcel; 971
Curlin, Marcel E.; **986**, **1026**
Curran, Adria; 714
Curran, Kelly; 1086, 1087, 1086, 1087
Currier, Judith S.; 31LB, 140, 515
Cusato, Jessica; 791
Custodio, Joseph M.; **951**
Cuzin, Lise; 575, **1009**
Cysique, Lucette A.; **437**, 441, 505

– D –

D.M. Kashuba, Angela; 535, 535
D'Agostino, Ralph B.; 751, 751
d'Arminio Monforte, Antonella; 303, 142, 303, 562, 636, 637, 705, 739, 805
D'Avolio, Antonio; 791
D'Ettorre, Gabriella; 296
Daar, Eric S.; 300
Daar, Eric; 304
Daar, Eric S.; 300
Daar, Eric; 304, 330, 517
Dabis, François; 103LB, 563, 576, 582, 807
Dadabhai, Sufia; 869, 1047
Dadaille, Rita T.; **1012**
Dadem, Nancin; 1075
Dagnra, Claver; 807
Dahari, Harel; 708LB
Dai, James; 979
Dalmau, Judith; 283
Damond, Florence; 230, 891
Dan, Jennifer M.; **300**, **300**, 330
Danaviah, Siva; 256, 248, 256, 603
Dancel-Manning, Kristen; 46LB
Danel, Christine; **115LB**, 544
Dansereau, Emily A.; **584**
Darilay, Annie; 797
Darin, Kristin M.; 85LB, 940
Darling, Katharine; 675
Darragh, Teresa; 713
Darty, Melanie; 564
Darwinkel, Marianne; 102
Das, Atze; 540
Dash, Prasanta K.; 504, 528, **543**
Dat, Tran; 922
Dattez, Sophie; 512
Daughtridge, Giffin W.; **975**
Däumer, Martin; 336, 431, 605
Davalos, Albert R.; 722
Davenport, Miles; 363
David, Matthew; 1089, 1089
David, Nkiru; 940
Davidson, Alan; 724, 724
Davies, Graham; 798
Davies, Mary-Ann; 563, **920**
Davis, Nicole L.; **886**
Day, Jeremy; 843
Day, Tyler R.; **456**, 496, 499
Daza, Glenda; 617, 627
de Bree, Godelieve; 1007
de Andrade, Angela; 856
De Angelis, Daniela; 1117
de Armas, Lesley R.; **947**
de Castro, Elisa; 43, 187
De Groote, Mary A.; **309**
De Jesus, Paul; 40, 43
de Jong, Dorien; 403
de Jong, Ype P.; 644, 644
De la Torre, Antonio; 58
De Luca, Andrea; 562
de Mendoza, Carmen; 594, 602
de Oliveira, Tulio; **256**, **248**, **256**, **603**, 991LB
De Oliveira, Fabienne; 232, 233
de Pablo, Carmen; 735
De Paris, Kristina; 948
de Pundert, Marieke E.; **574**
de Rekeneire, Nathalie; 103LB
De Rijck, Jan; 198
De Rossi, Anita; 919, 923
De Silva Feelixge, Harshana S.; 400
De Sousa, Mailys; 949
de Sousa Muhate, Amina M.; **615**
de Souza, Mark; 272
de Spiegelaere, Ward; 377, 424, 549
de Vente, Jerome; 554LB
de Vlas, Sake J.; 159
De Wit, Stéphane; 315, 739, 805
de Wolf, Frank; 252, 1117
Deanfield, John; 37
Deayton, Jane R.; **332**
Debanne, Sara M.; 137, 745, 771
Debes, Rachel; 747, 747, 997
Debyser, Zeger; 198, 611
Decalf, Jeremie; 681
deCamp, Allan; 55LB
Decaris, Martin L.; 299LB
DeCenso, Brendan; 584
Decker, Timothy; 44
Decroix, Nipa; 329
Deeks, Steven; 210, 267
Deeks, Steven G.; 299LB
Deeks, Steven; 362
Deeks, Steven G.; 382
Deeks, Steven; 386, 428LB
Deeks, Steven G.; 430
Deeks, Steven; 752, 755, 757, 759, 760, 763, 784
Degaffe, Guenet; 922
Dehovitz, Jack A.; 516
Dejesus, Paul; 288
DeJesus, Edwin; 113LB
DeJesus, Erin; 434
del Amo, Julia; 1051
Del Bello, David; **647**
Del Bianco, Paola; 919
del Rio, Carlos; 973, 1068, 1074
Del Río-Estrada, Perla; 49, 167, 326
Dela Cruz, Mark L.; **757**
Delagreverie, Heloise; **429**
Delaney, Kevin P.; **621**
Delany-Moretlwe, Sinead A.; 26LB
Delaporte, Eric; 782, 782, 793
Delaugerre, Constance; 429, 706
DelBianco, Gabriela; 922
Delfraissy, Jean-Francois; 23LB
Delino, Nicole S.; 537
Dellamonica, Pierre; 1009
Delobel, Pierre; 274, 814
Delong, Allison; 597
Delpech, Valerie; 154, 253
Demarest, James F.; 633
DeMasi, Ralph; 551
DeMaster, Laura; **390**, **390**
Demeulemeester, Jonas; 198
Demirci, Utkan; 421LB
Dempsey, Antigone; 1064
Deng, Kai; 368
Deng, Qianqian; 462
Deng, Xutao; 386
Dennis, Ann M.; 242
Denny, Thomas; 258, 258, 904
Dermody, Nadene; 437
Deroo, Sabrina; 213
Derrico, Monica; 856
Dervillez, Xavier; 213
Deryabina, Anna; **176**, **1029**
Desai, Mitesh A.; **632LB**
Desai, Seema N.; 676, **1050**
Deshmukh, Savitha; 407
Desinor, Olbeg; 875
Desnoyer, Aude; 723
Detels, Roger; 490
Deutsch, Reena; 497
Devaux, Carole; 213
Deville, Jaime G.; 954
Dewar, Robin; 48
Deya, Ruth; 853
Deyà-Martínez, Àngela; 934
Deymier, Martin; 54LB
Dezzutti, Charlene; 994
Dhanireddy, Shireesha; 1092
Di Biagio, Antonio; 442
Di Giallonardo, Francesca; 255, 255
Di Giambenedetto, Simona; 495, 655
Di Gregorio, Adriana; 776
Di Maio, Velia Chiara; 699
Di Paolo, Daniele; 699
Di Perri, Giovanni; 487, 791
Di Pietro, Massimo; 655
Di Sora, Fiorella; 442
Diallo, Alpha; 146
Diallo, Mohamadou Saliou; 1077
Dibb, Zoe; 851
DiCarlo, Abby L.; 1103
DiCarlo, Lorenzo; 828LB
DIckens, Alex; 497
Dicker, Ira B.; 114LB, **539**
Dickinson, Laura; 532, 532
Didier, Céline; 52
Diep, Brian; 365
Diero, Lameck; 597
Dieterich, Douglas; 149, 151LB, 152LB, 648, 647, 648
Dietz Ostergaard, Sharon; 862
Diez, Cristina; 682
Díez-Pérez, Adolfo; 767
Dillon, Stephanie; 186, 262
Dilly-Penchala, Sujan; 85LB
DiMeglio, Linda A.; 931
Dimitri, Justeau; 1077
Dinarello, Charles; 405
Dinesha, Thongadi Ramesh; 704
Ding, Song; 422
Dinh, Chuong; 963, 993
Diouf, Assane; 782, 782, 793
Dirajlal-Fargo, Sahera; **745**
Dirks, Miriam; 431
Dittmer, Ulf; 186
DiTursi, Sara; 542
Dlamini, Sarah; 984
Do, Viet Chau; 956
Dobard, Charles W.; **963**, **993**
Dobrowolski, Curtis; 404
Dobs, Adrian; 786
Dodge, Jennifer L.; 639
Doherty, Irene A.; 852
Doitsh, Gilad; **202**, **202**
Dolan, Matthew; **581**
Dollfus, Catherine; 334, 867
Dombrowski, Julia C.; 1061, 1061, 1066, 1093, 1099
Dombrowski, Julie; 1092
Domercant, Jean W.; 875
Domingo, Pere; 767
Doms, Robert; 349
Doncel, Gustavo F.; 26LB
Dong, Krista; 339, 359
Dong, Winnie; 592, 697
Donnachie, Elizabeth; 922
Donnell, Deborah; 24, 29, 290, 981, 989, 1013, 1095
Dooley, Kelly E.; **907**
Dore, Gregory; **180**, 688
Dorfman, David; 446
Dorfman, Jeffrey; 231
Dorrell, Lucy; 377
Dorsey, Grant; 883
Dortenzio, Eric; 1077
Dosekun, Olamide; 961, 961
Douek, Daniel C.; 47
Douek, Daniel; 394
Douglas, Pamela; 750, 750
Down, Carrie; 644, 644
Doyle, Tomas J.; **594**
Dragavon, Joan; 617, 627

Drake, Alison L.; **866**, **866**
Drexler, Dieter; 539
Drexler, Jan F.; 849
Drozd, Daniel R.; **748**, **748**, 749LB, 804, 1005
Drummond, Fraser; 633
Dryden-Peterson, Scott; **711**, 718, 878
Drylewicz, Julia; 549
Du, Victor; 364
Duarte, Rafael; 432
Dube, Michael; 254
Dube, Michael P.; 300
Dube, Michael; 304
Dube, Michael P.; 140
Dube, Michael; 254
Dube, Michael P.; 300
Dube, Michael; 304
Dube, Michael P.; 330
Duber, Herbert C.; 584, 617
Dubrow, Robert; 728, 728
Duenas-Decamp, Maria; **216**
Duffill, Kathy; 994
Duffy, Darragh; 681
Dufour, Cécilie; 701
Dufour, Jean-François; 150
Dugust, Anne-Sophie; 339
Dukuze, Adeline; 157
Dumas, Hervé; 814
Dunais, Brigitte; 650
Dunaway, Shelia; 479, 840
Duncan, Melanie R.; **502**
Dunleavy, Kieron; 399
Dunn, David; 22LB, 253, 594, 596
Dunn, Liezl; 604
Dunne, Eileen F.; **855**, 1026
Dunning, Lorna; 34
Dunsmore, Tammy; 406, 965
Dupin, Nicolas; 723
Dupke, Stephan; 671
Durand, Christine M.; 380, 419
Durant, Jacques; 650
Durham, Marcus; 997
Durham, Natasha D.; **220**
Dusabe, Eric; 157
Dusingize, Jean Claude; 780, 780
Duval, Xavier; 139
Duvivier, Claudine; 575
Dvali, Natia; 664
Dybul, Mark; 1114, 1114
Dye, Bonnie; 978LB

– E –

Easterbrook, Philippa; 595
Easterbrook, Philippa; 1072
Eaton, Jeffrey; 161
Eberhardt, Kirsten A.; 849
Ebrahimi Mohammadi, Diako; 363
Echeverria, Patricia; 767
Eckard, Allison R.; **925**
Edén, Arvid; **474**
Efstathiou, Jason; 711
Egger, Matthias; **724**, 563, **724**, 808, 1117
Eggman, Ashley A.; 1113
Eholie, Serge; 115LB
Eholié, Serge P.; 544, 576
Ehrenkranz, Peter; 155, 938, 1013
Eisele, Lewin; 568
Ekouevi, Koumavi K.; 576, 807
El Antouny, Neveen; 800
El-Diwany, Ramy; **685**
El-Sadr, Wafaa M.; **29**, 739, 1029, 1095, 1100, 1103
Eleanor, Wilson; 653
Eleftherios, Michailidis; 585
Eley, Brian; 724, 724, 920
Elford, Jonathan; 560
Elharrar, Vanessa; 978LB
Elion, Richard A.; **128**
Elion, Richard; 749LB
Elion, Rick; 29
Elkington, Paul T.; 811
Ellenberg, Susan; 308
Eller, Michael A.; 166
Ellerbrock, Tedd V.; 155, 938
Ellington, Sascha R.; **868**, 886
Elliott, Julian; 281
Elliott, Julian H.; **428LB**
Elliott, Julie; 289, 994
Ellis, Angela; 931
Ellis, Jayne; 335
Ellis, Michael; 847
Ellis, Ronald J.; 58, 435, 436, 460, 461
Ellis, Ronald; 462
Ellis, Ronald J.; 469, 491, 496
Ellman, Tanya M.; **1013**
Ellman, Thomas; 32, 555, 1014
Ello, Frederic; 544
Elloumi, Fathi; 197
Elopre, Latesha E.; **1004**
Else, Laura; 85LB, 86LB, 533, 533, 964
Elzi, Luigia; 531, 531
Emerman, Michael; 41, 203, 194, 203
Emerson, Ruth; 1013
Emery, Sandy; 866, 866
Emery, Sean; 779, 315, 779
Emery, Vincent; 884
Emiliani, Stephane; 540
Emson, Claire; 299LB
Ende, Zachary; **54LB**
Engels, Eric A.; 725, 717, 725
Engle, Liz; 476
Ens, Carla; 1054
Epelboin, Sylvie; 1122
Epie, Fanny; 880
Erasmus, Linda; 823
Erdmann, Nathaniel B.; **364**
Erkizia, Itziar; 283
Erlandson, Kristine M.; **778**, **771**, **778**
Eron, Joseph J.; 112LB, 147
Eron, Joseph; 439
Eron, Joseph J.; 440
Eron, Joseph; 445
Eron, Joseph J.; 691, 769LB, 1005
Esaki Muthu, Shankar; **820**
Escota, Gerome; 772
Escudero, Daniel; **1116**
Eshleman, Susan H.; 116, 622, 622, 623, 629, 869
Espiau, Maria; 950
Espinoza, Lorena; 999, 1000, **1040**
Espluges, Juan V.; **500**
Esplugues, Juan; 735
Esposito, Anthony; 323
Esposti, Sandra; 1010
Essat, Asma; 373
Esser, Stefan; 431, 568
Essex, Max; 247, 630, 878, 990
Esté, José; 204, 205
Estes, Jacob D.; 286
Esteve, Anna; 837, 837
Estrach, Teresa; 845
Estrada, Vicente; 266
Estrella, Michelle M.; 797
Etard, Jean-François; 32, 153, 625, 555, 624, 625, 1014, 1079, 1090
Etemad, Behzad; 110LB, 217
Ethridge, Steven F.; 613
Ethridge, Steven; 621
Ethridge, Steven F.; 1100
Eudailey, Josh; 903
Eugen-Olsen, Jesper; 316
Eugenin, Eliseo; 211
Euler, Zelda; 339, 411
EuroCoord, EuroSIDA in; 561
Evans, Charlesnika; 676
Evans, Denise; 781, 781
Evans, Scott; 451, 710
Evans, Vanessa A.; 388
Evans-Strickfaden, Tammy; 860, 855, 860
Evering, Teresa H.; 305, **446**
Everson, Greg; 81, 652
Eyawo, Oghenowede; 1055
Eymard-Duvernay, Sabrina; 782, 727, 727, 782, 793

– F –

Fabbiani, Massimiliano; 495
Facente, Shelley; 626, 626
Faesen, Mark; 89
Fagan, Jennifer L.; 1057
Fairley, Christopher; 281
Fajardo, Emmanuel; 555
Fakoya, Ade; 1114, 1114
Falco, Vicenç; 714
Falcón-Neyra, Lola; 934
Faldetta, Kimberly F.; **812**, 813
Fankuchen, Olivia R.; **340**
Faria de Oliveira, Michelli; 58, 375, **435**, **491**, 496
Farokhzad, Omid; 357
Farquhar, Carey; 945, 946, 989, 1035
Farrar, Jeremy; 843
Farrior, Jennifer; 1095
Farshy, Carol; 963
Farzan, Michael; **163**
Farzaneh-Far, Ramin; 784
Fast, Pat; 1044
Fatti, Geoff; 920
Fauchet, Floris; 949
Fauci, Anthony S.; 340
Faulds, Samantha; 651, 651
Fawzi, Wafaie; 606, 809
Faye, Albert; 867
Fayorsey, Ruby; 914
Fazeli, Pariya L.; **483**, 484
Febo, Irma; 269
Fedida, David; 536
Fedoriw, Yuri; 535, 535, 719
Feeney, Eoin; 677
Feldmann, Anna; **343**
Feldt, Torsten; 849
Fellay, Jacques; 291, 293
Fellows, Lesley K.; 469
Felton-Coleman, Angela; 84
Feng, Hwa-Ping; 522
Feng, Pei-Jean; 827LB
Fennelly, Glenn; 948
Fennema-Notestine, Christine; 461, 462
Fenton, Terrence; 924
Fenton-May, Angharad; 54LB
Fernández McPhee, Carolina; 918, 942
Fernández-Romero, José; 967, 968
Fernandez-Sesma, Ana; 187
Ferrando-Martinez, Sara; 49, 167
Ferrando-Martínez, Sara; 266
Ferret, Samuel; 779, 139, 779
Ferretti, Francesca; 442, **443**
Fetogang, Ernest; 990
Feyertag, Felix; 230
Fibriani, Azzania; 566
Fichtenbaum, Carl; 769LB
Fidler, Sarah; 111LB, 961, 961
Fiedler, Tina L.; 861, 861
Fielding, Katherine; 823, 825
Fielding, Katherine L.; 885
Fields, Sheldon D.; 116, 1017
Fierer, Daniel; 647
Fievez, Virginie; **213**
Figg, Douglas; 87
Figoni, Julie; 831
Filali, Ali; 292
Filteau, Suzanne; 762
Finlayson, Robert; 733
Finlayson, Teresa; 1060, 998, 1060
Finn, Erin E.; **834**, **834**
Firnhaber, Cynthia; **89**, 710, 824
Fischer, Rebceca; **846**
Fischl, Margaret A.; 273, **310**, 337
Fiscus, Susan A.; 31LB, 909
Fishbein, Dawn A.; 666
Fisher, Martin; 961, 768, 961
Fisher Raymond, Henry; 1025
Fiske, Christina; **900**
Fitch, Kathleen; 136
Fitch, Kathleen V.; 138
Fitzgerald, Daniel; 156, 546
Fitzgerald, Naomi; 961, 961
Fitzmaurice, Garrett; 1080
Fitzpatrick, Meghan; 490
Flavell, Richard; 368
Fleishman, John; 1104, 1065, 1104
Fletcher, Courtney; 84, 436, 511
Fletcher, James L.; 48, 473, 480
Flores, Juan; 1122
Flores, Norma; 607
Floridia, Marco; 879
Fluharty, Tayler; **290**
Foca, Marc; 930
Fogel, Jessica M.; **629**, 869
Foissac, Frantz; 863, 863, **949**
Fokar, Ali; 868, 909
Folkvord, Joy; 859, 426, 859
Fong, Siew; 915
Fontas, Eric; 739
Ford, Nathan; 1011, 1118
Ford, Susan; 966LB
Fordyce, Marshall W.; 143LB, **795**
Forgione, Lisa; 239
Formaglio, Pauline; 285
Forner, Alejandro; 640
Forrest, Jamie I.; 1025
Fortes-Deguenonvo, Louise; 782, 782

Fortuny, Clàudia; 923, **934**, 950
Foster, Rosalind; **958**, **958**
Fouda, Genevieve; **903**, 904, **905**
Foulds, Kathryn; 50
Fowler, Mary Glenn; **31LB**
Fox, Julie; **86LB**, 961, 961
Fox, Matt P.; **781**, **781**, 1091
Fox, Matthew P.; 571, 1120
Fox, Steven; 449
Fraenkel, Liana; 790
Francischetti, Ivo; 268
Francois, Kesner; 875
Frank, Bruce; 992LB
Frank, Daniel N.; 262
Frank, Ian; 112LB
Franklin, Donald; 56, 456, 460, 462, 474, 483
Frantzell, Arne; 121, 696
Fraser, Christophe; **127**, 249, **252**, 1048, 1117
Frater, John; **111LB**, 818
Frederix, Koen; 1103
Fredrick, Linda; 147
Fredricks, David N.; 861, 861
Freedberg, Kenneth A.; 93
Freedberg, Kenneth; 1104, 1119
Freedberg, Kenneth A.; 844, 1015
Freedberg, Kenneth; 1104, 1119
Freedman, Jane E.; 759
Freedman, Mark; 1057
Freeman, Michael L.; 298LB
Fregoso, Oliver I.; **41**
Freguja, Riccardo; **919**
Freiberg, Matthew S.; 746, 565, 746, 1049
Freire, Marcos; 318
Freitas, Lorri; 1020
French, Audrey; 639
French, Audrey L.; **676**, 1050
Frenkel, Lisa; 107, 250, 983, 1081
Frey, Christian R.; 530
Frezieres, Ron; 995
Frias, Mario; 709
Friedland, Jon S.; 811
Friedman, Ruth; 856
Friedman, Sam; 1006, 1070
Friedman, Samuel; 1116
Friedrich, Nikolas; 351
Friis, Henrik; 762
Frison, Lawrence; 854
Frohnen, Patricia; 226
Fromentin, Remi; 388, 413
Fuchs, Dietmar; 59, 60, 470, 474
Fuertes, Irene; 845
Fujii, Nobutaka; 589
Fujimoto, Katsuya; 210
Fujiwara, Esther; 471
Fulcher, Jennifer A.; **289**
Funderburg, Nicholas; 298LB
Funes, Haryes A.; 500
Furrer, Hansjakob; 837, 315, 837
Fux, Christoph; 142, 742
Fyne, Elizabeth; 379, 105, 106, **371**, 379, 398

– G –

Gaardbo, Julie C.; 325, 758, 803
Gabillard, Delphine; 115LB
Gabuzda, Dana H.; 498
Gagliardini, Roberta; 442
Gaillard, Jean-Louis; 232
Gaisa, Michael M.; 90, 715
Gakidou, Emmanuela; 584, 617
Galardi, Cristin; 538
Gale, Michael; **79**
Galea, Sandro; 1116
Galicier, Lionel; 429
Gallart, Teresa; 354
Galli, Laura; **442**, 443, 773
Galli, Massimo; 562
Galloway, Nicole; 202, 202
Galluzzo, Clementina; 879
Gama, Lucio; **416**
Gamble, Theresa; 29, 1100
Gamieldien, Hoyam; 314, 857
Gandhi, Monica; **514**, 516, 792, 887, 1050
Gandhi, Neel R.; 92
Gandhi, Rajesh T.; 110LB, 378
Ganesan, Anuradha; 565
Gange, Stephen J.; **9**, 726, 516, 726, 749LB, 996, 1053
Ganz, Peter; 731, 755, 757, 759
Gao, Feng; 258, 258
Gao, Hongmei; 346
Gao, Qin; 513
Gao, Yong; 215
Garbis, Spiros D.; 409
Garcel, Aude; 104LB
Garcia, Elisabet; 964
Garcia, Federico; 594
Garcia, Felipe; 391, 959, **354**, 391, 959, 960
Garcia, J. Victor; 425
Garcia Lopez-Hortelano, Milagros; 942
García-Álvarez, Mónica; **682**
Garcia-Lerma, Gerardo; 962
Garcia-Morales, Claudia; **601**, 607
García-Navarro, Cristina; 937
Garcia-Sastre, Adolfo; 43, 187
Garcia-Tsao, Guadalupe; 656
Gardiner, Elizabeth E.; 736
Gardner, Edward M.; 83, 525
Gardner, Kristian; 785
Gardner, Lytt I.; **101**
Gardner Toren, Katelynne M.; 238
Gareta, Dickman; 1102
Garfein, Richard R.; 246
Garg, Ankita; **301**, **301**
Garg, Shikha; **974**
Garmon, Donald; 446
Garraffo, Rodolphe; 650
Garrett, Nigel; 984, 987
Garrido, Carolina; **372**
Garrison, Kimberly; 82
Garrison, Louis; 712
Garvie, Patricia; 450
Gasasira, Anne; 617
Gaseitsiwe, Simani; 630
Gasper, Melanie; 279
Gatanaga, Hiroyuki; 328
Gatell, Jose M.; 959, 354
Gatell, Jose; 637
Gatell, Jose M.; 959, 960
Gatell, Josep M.; 845
Gates, Thomas M.; 441
Gathogo, Esther N.; **798**
Gatserelia, Lana; 664
Gaudin, Francoise; 723
Gauguier, Dominique; 138
Gaur, Aditya; 951, 953, 954
Gauthier, Pierre-Arnaud; 213
Gavegnano, Christina; **418**
Gavryushkina, Alexandra; 252
Gay, Cindy L.; 620, 1018
Gay, Cynthia L.; 1003
Gaye, Oumar H.; 1078
Geary, Rebecca; 1107
Gebi, Usman I.; 558
Gebo, Kelly; 726, 1104, 726, 996, 1065, 1104
Geboy, Alexander G.; **666**
Geffner, Mitchell; 880, 931
Geijtenbeek, Teunis; **124**
Gelbard, Harris; 543
Geleziunas, Romas; 108
Gelman, Benjamin B.; **61**, 483
Genberg, Becky L.; **1073**, 1075
Gendelman, Howard; 504, 528, 529, 543
Geng, Elvin H.; 1072
Geng, Xin; 202, 202
Gentile, Massimo; 296
George, Alvin; 214
George, Noble; 482
George, Varghese; 310
Georgiev, Ivelin; 170LB
Gerard, laurence; 429
Geretti, Anna Maria; 594
Gerevini, Simonetta; 443
Germain, Ronald; 167
German, Polina; **82**
Gerner, Michael; 167
Gerstoft, Jan; 758, 803
Gessain, Antoine; 237
Gettie, Agegnehu; 968
Geurtsen, Gert J.; 472, 935
Ghannoum, Mahmoud A.; 844
Gharib, Ahmed; 928
Ghosn, Jade; 373
Ghuschcyan, Vahram; 652
Gianella, Sara; 391, 330, 391, 435, 491, 492
Gianella Weibel, Sara; 300, **304**, **58**, 219, 300, **304**, **375**, 496, **1020**
Gianesin, Ketty; **923**
Giaquinto, Carlo; 919, 923
Giardiello, Marco; 527
Gibb, Diana M.; 35, 37, **78**, 919, 927, 941
Gibbert, Kathrin; 186
Gibert, Cynthia; 728, 141, 656, 728, 1049
Gibson, Gregory; 188, 188
Gibson, Steven; 25
Giddy, Janet; 93
Giganti, Mark J.; 580
Gijsbers, Rik; 198
Gilbert, Mark; 1023, 1024
Gilbert, Peter; 51
Gilbert, Peter B.; 55LB
Gile, Jillian; 286
Gill, Alexander J.; **501**, 502
Gill, John; 448, 465, 467, 471, 579, 602, 996, 1053
Gill, Michelle; 865, 865
Gill, Noel; 618
Gilleece, Yvonne; 768
Gilmore, Jody; 645, 645
Gllson, Richard; 560
Gingo, Matthew; 490
Giordano, Frank A.; 381
Giordano, Thomas; 101
Girard, Pierre-Marie; 544, 706, 766
Girouard, Michael P.; 1119, 1119
Gish, Robert; 661
Gisslén, Magnus; 59, 62, 470, 473, 474
Giuliani, Ruggero G.; 153, 555, 1079
Giuliano, Marina; 879
Giuseppe, Pantaleo; 352
Giustini, Noemi; 296
Givens, Naomi; 550
Gjerdrum, Lise Mette R.; 325
Glässner, Andreas; 678, 679, 680
Glenn, Jeffrey; 708LB
Glesby, Marshall; 639
Glidden, David; 25
Glidden, David V.; 83, 88, 514, 722, **970**
Glowa, Thomas; 651, 651
Glynn, Judith R.; **816LB**, 885
Go, Vivian F.; 851
Godfrey, Catherine; 310, 710
Goedert, James J.; **68**, 197, 1053
Goedhals, Dominique; 818
Goeieman, Bridgette; 89
Goeken, Nolan; 254, 254
Goepfert, Paul A.; 364
Goeser, Felix; 679
Goetz, Matthew B.; 728, 746, 728, 746
Goffinet, Christine; 395
Gogia, Shawn; **784**
Golden, Matthew R.; 1061, 238, 1061, 1066, 1092, 1093, **1099**
Goldhaber-Fiebert, Jeremy D.; 1121
Goldstone, Stephen; 715
Goliath, Rene; 811
Golub, Elizabeth; 858, 639, 858
Golub, Elizabeth T.; 1050
Gomes, Perpétua; 610
Gómez, Elisabet; 331
Gonçalez, Thelma T.; 1010
Gonzalez, Ana; 845
Gonzalez, Oscar A.; 217
Gonzalez Perez, Juan; 577
González Tomé, Maribel; 942
González-Cordón, Ana; 959, 959
González-Moreno, Juan; 553
Gonzalez-Serna, Alejandro; **117**
Gonzalez-Tome, Maria Isabel; 918, 950
González-Tomé, María Isabel; **937**
Goodenow, Maureen M.; 183
Gooneratne, Shayarana; **363**
Gopal, Ramya; 284
Gopal, Satish; **719**, 721
Gorantla, Santhi; 504, 528, 543
Gorbach, Pamina; 672, 1033
Gordin, Fred; 1095
Gordon, Ana; 709
Gordon, Daniel E.; 599
Gordon, Daniel; 1002
Gordon, Kelley C.; 985
Gordon, Kirsha; 728, 728
Gordon, Lori A.; 692
Gorelick, Robert; 420
Gorgievski, Meri; 336
Gori, Andrea; 466, 655
Gori, Caterina; 611
Gorry, Paul R.; 633
Gorstein, Jonathan; 945

Goryo, Mai; 590
Gosalbes, María José; 266
Gottlieb, Geoffrey S.; 541, 588, **614**
Gotuzzo, Eduardo; 833
Götz, Hannelore M.; 1105
Gouaux, Ben; 464
Gougeon, Marie-Lise; 285
Goujard, Cécile; 333, 373
Goulder, Philip J.; 362, 921
Gouzil, Julie; 237
Govender, Tessa; 93
Govender, Vaneshree; 1033
Grabowski, Mary K.; **28**, 30, **1084**
Grabowski, Mary; 622, 622
Grabowski, Mary K.; **1084**
Graham, Lisa; 835, 835
Graham, Susan M.; 102
Grand'Pierre, Reynold; 875
Granich, Reuben; 1112
Granier, Catherine M.; **550**
Grant, Alison; 823, 825
Grant, Igor; 436, 460, 462, 474, 483, 484, 491, 492, 497
Grant, Jennifer L.; 649, 649
Grant, Robert M.; **25**, 83, 514, 970, 977
Grant, Robert; 978LB
Gras, Luuk; 566, 674, 1007, 1048
Grasso, Chris; 972
Graversen, Mette E.; 369
Gray, Glenda; 26LB, 292, 629
Gray, Lachlan R.; 633
Gray, Ronald H.; 28, 30, 1084, 1088, 158, 622, 321, 452, 453, 454, 458, 622, 1036, 1084, 1085, 1088
Greathead, Louise; 477
Green, Keith; 1070
Green, Nella L.; **240**, 1021, 1022
Green, Richard M.; 649, 649
Greenberg, Alan; 660
Greenblatt, Ruth M.; 858, **294**, 792, 858
Greene, Elizabeth; 1100
Greene, Kelli; 346
Greene, Warner C.; 202, 202, 208, 209, 385
Gregory, Philip D.; 433
Greig, Jane; 1011
Grey, Jeremy; 1115
Griffith, Sandy K.; 554LB
Grima, Pierfrancesco; 495
Grinspoon, Steven; **134**, 136
Grinspoon, Steven K.; 138
Grinspoon, Steven; 751, 734, 751
Grinsztejn, Beatriz; 1119, 514, 824, 856, 1019LB, 1119
Grint, Daniel; 637
Grooms-Williams, Tiffany; 350
Gross, Chloe; 692, 694, 695
Gross, Robert; 810
Grosskurth, Heiner; 94
Grossman, Cynthia; 979
Groves, Katherine C.; 332
Grulich, Andrew E.; **1019LB**
Grund, Birgit; 761
Grunfeld, Carl; 804
Guanira, Juan; 514, 977
Guaraldi, Giovanni; 773
Guardado, Maria Elena; 1032
Guardo, Alberto C.; **960**
Guay, Laura; 865, 865
Guedj, Jérémie; **148**
Guelar, Ana; 714
Guerra, Vitor C.; **882**
Guerra-Assunção, José Afonso; 816LB
Guerrero, Santiago X.; 193
Guida, L Anthony; 83
Guida, L. Anthony; 525
Guillén, Yolanda; **260**, 261
Guillerme, Jean-Baptiste; 329
Guillouet de Salvador, Francine; 575, 650
Gulick, Peter; 147
Gumbi, Pamela; 314
Gummuluru, Rahm; 188, 188, 222
Gunaratna, Nilupa S.; 809
Gunn, Roger; 477
Günthard, Huldrych F.; 255, 199, 218, 244, 245, 253, 255
Guo, Dongwei; **529**, 543
Guo, Haitao; 327
Guo, Kejun; 186
Guo, Qi; 477
Guo, Zifang; 522
Gupta, Amita; 778, **132**, 313, 567, 778, 1108
Gupta, Samir K.; **737**, 795
Gupta, Swati; 372
Gupte, Nikhil; 778, 313, 567, 778
Gussio, Maria; 776
Gustafson, Deborah; 294, 770, 775
Guthrie, Brandon L.; 1035
Gutierrez, Mar; 767
Guzmán-Fulgencio, María; 682
Gvetadze, Roman; 635, 1082
Gwynn, Charon; 1029

– H –

Haaland, Richard E.; **860**, **860**
Haas, Andreas D.; **563**
Haas, David W.; 515, 517
Haazen, Wouter; 524
Haberer, Jessica; 24, 317
Haberer, Jessica E.; **556**
Haberer, Jessica; 976, 980, 988
Hadigan, Colleen; 756, 928
Hagberg, Lars; 59, 62, 470
Hager, Cindy; 900
Hagins, Debbie P.; 554LB
Hahn, Beatrice H.; 44, 169
Haidari, Goli; **961**, **961**
Hakim, James; 57, 119, 313, 451
Hakim, James G.; **552**
Hakim, James; 844
Hall, Breana M.; 55LB
Hall, H. Irene; 29, 100, 120, 241, 578, **999**, **1000**, 1040, 1052, 1115
Hall, Laura; 620, 1018
Hall, Matthew; 249
Hallack, Renee; 664
Hallett, Timothy; 1111, 1107, 1111
Halue, Guttiga; 511, 788
Halupnick, Ryan; 826
Halvas, Elias; 106
Halvas, Elias K.; 982
Ham, Anthony; **510**
Ham, David; **1032**
Hamanishi, Kristen A.; 985
Hamers, Raph L.; 557, 574
Hamlyn, Elizabeth; 111LB
Hammarskjold, Marie-Louise; 201
Hammer, John; 713
Hammer, Scott M.; 55LB
Hamorsky, Krystal; 350
Hamouda, Osamah; 1051
Hamzah, Lisa; 768, **794**
Han, Larry; 1096
Han, Yang; 790
Hanchett, Jesse; 542
Hangai, Fatima; 1010
Hanhauser, Emily; 421LB, 430
Hanifa, Yasmeen; **823**
Hanna, David B.; **729**
Hanna, George J.; 509, 523, 545
Hans, Lucia; 910
Hanson, Barbara; 319
Hanson, Debra; 862, 962
Hansson, Kyra; 459
Hansudewechakul, Rawiwan; 915, 943
Haour, Georges; 701
Harada, Shigeyoshi; **590**
Haraguchi, Kazuhiro; 537
Harb, Socorro; 627
Harber, Mark; 798
Hardin, Dana; 954
Hardin, Royce; 787
Hardy, Isabelle; 251
Harkoo, Ishana; 1033
Harper, Lynda; 919
Harper, Michael; **186**
Harrigan, Richard; 117, 291, 592, 598, 697
Harrington, Robert; 1092
Harris, Shericka; 1000
Harrison, Linda J.; 310
Hart, Clyde E.; 860, 860
Hart, Rachel; 660
Hartogensis, Wendy; 209, 428LB
Harton, Marisa; 309
Harty, Alyson; 149
Harvey, Katherine L.; 633
Harvill, Kara; 299LB
Harwood, Katherine; 141
Hasselrot, Klara; 287
Hassounah, Said; **591**
Hatano, Hiroyu; 299LB, 382
Hataye, Jason M.; **394**
Hatch, Steven C.; 45
Hatleberg, Camilla I.; **582**, **739**
Hatzakis, Angelos; 229
Haubrich, Richard; 300, 304, 300, 304
Haubrich, Richard H.; 330
Haubrich, Richard; 828LB, 926, 929
Hauck, Heather; 1064
Haughey, Norman J.; **497**
Hauser, Blake; 112LB
Häussinger, Dieter; 849
Havlir, Diane; 210, 309, 740, 824, 883, 887, 1056, 1071, 1101
Hawkins, Claudia; **649**
Hawkins, Claudia A.; **606**
Hawkins, Claudia; **649**
Hawkins, Trevor; 434
Haynes, Barton; 355, 903, 905
Hazra, Rohan; 882, 917, 928, 931, 933
Hazuda, Daria; 449
He, Tianyu; 268
Heal, David; 1099
Heaps, Jodi M.; 447, 488
Heath, Katherine; 1118
Heath, Sonya L.; 364
Heaton, Robert; 56, 444, 456, 462, 469, 474, 478, 483
Hebbeler, Andrew; 385
Hébélamou, Jean; 103LB
Hecht, Frederick M.; 209, 382
Hecht, Jen; 25
Hechter, Rulin C.; **842**
Heckbert, Susan R.; 748, 748
Heffron, Renee; 24, **969**, 1106
Heidersbach, Amy; 385
Heimburger, Douglas; 762
Heintschel von Heinegg, Evelyn; 568
Hellar, Augustino M.; **1086**, **1086**
Helleberg, Marie; 877
Heller, Theo; 708LB
Hellerstein, Marc K.; 299LB
Hellmuth, Joanna; 438
Hellstrom, Lize; 951
Hema, Arsene; 793
Hendrix, Craig; 978LB, 979, 988, 992LB
Hendrix, Craig W.; 994
Heneine, Walid; 120, 962, 963, 993
Henessey, Kelley; 1012
Henning, Tara; 962, 963
Henrich, Timothy J.; 421LB, 430
Henry, Keith; 713
Hensley-McBain, Tiffany; **286**
Herbeck, Joshua; 51
Herbeck, Joshua T.; 238
Herbeck, Joshua; **250**
Herbst, Kobus; 1110, 161, 248, 583, 896, 1102, 1110
Herbst, Philip; 926
Herce, Michael E.; **721**, **874**
Heresi, Gloria P.; 922
Herlihy, Therese; 732
Hernandez, Angela L.; 100, 120, 241, 1043
Hernandez-Romieu, Alfonso C.; **789**
Herold, Betsy; 992LB
Herrera, Carolina; 86LB, 287
Hesney, Michael; 523
Hess, Kristen; 1041
Hesselgesser, Joseph; 108
Hesseling, Anneke C.; **133**
Hew, Huong; 697
Hewlett, Indira; 258, 258
Hey-Cunningham, William; 437
Hezode, Christophe; 688
Hick, Chazha; 871
Hickman, Taylor; 185
Hiener, Bonnie; 109
Hightow-Weidman, Lisa; 1003
Hightow-Weidman, Lisa B.; 1018
Hilaire, James; 528
Hildreth, James E.; 214
Hileman, Corrilynn O.; **738**
Hill, Alison L.; 419
Hill, Andrew M.; **551**, **654**, **1118**
Hill, Shawn; 105, 420
Hillewaert, V; 893
Hilton, Rachel; 794, 798
Himes, Jonathan; 903
Hirsch, Vanessa M.; 503
Hirt, Deborah; 949
HIRT, Déborah; 512
Hladik, Florian; 366

Ho, David; 345
Ho, Emily; **479**, 840
Ho, Ya-Chi; **392**, **392**, 396
Hobbs, Kristen S.; 421LB
Hocqueloux, Laurent; 52
Hodara, Ariel; 81, 518
Hodcroft, Emma B.; **249**
Hodowanec, Aimee; **319**
Hoel, Hedda; 758
Hoelscher, Michael; 95LB, **131**
Hoen, Bruno; 575, 1009
Hoenderboom, Bernice M.; 118
Hoenigl, Martin; 240, **1021**, **1022**
Hoepelman, Andy I.; 243, 549
Hoffman, Heather J.; 865, 865
Hoffman, Irving F.; 851
Hoffman, Jennifer C.; 289
Hoffmann, Christopher J.; 822, 872, 907
Hoffmann, Jennifer D.; 822, 872
Hoffmann, Jennifer; 907
Hoffmann, Udo; 136
Hofmann, Christian; **365**
Hofstra, Marije; **243**
Hogan, John; 683
Hogan, Joseph; 597, 619, 1073
Hogg, Robert; 1023, 1024, 1025, 1053, 1055
Holder, Angela; 962
Holland, David; 827LB
Holman, Susan; 101
Holme, Molly P.; 630
Holmes, Michael C.; 433
Holodniy, Mark; 1121
Holtz, Timothy; 635, 1026
Hong, Feiyu; **379**, 106, **379**, 389LB, 398
Hontelez, Jan A.; **159**
Hood, Julia E.; **1066**
Hook, Edward; 1004
Hoots, Brooke E.; 855
Hoots, Brooke; **998**
Hoover, Donald R.; 780, 775, 780, 857
Hoover, Karen; **1082**
Hoppe, Anne; 57, 119, 552, 595
Hoque, Md. Tozammel; 534, 534
Horban, Andrzej; 637
Horberg, Michael A.; 996, 1053
Horng, Howard; 514, 887
Horning, Jayme; 529
Horsfield, Catherine; 794
Horwood, Paul; 1089, 1089
Hosein, Megan M.; **453**
Hosek, Sybil; 970
Hosmalin, Anne; 329
Hosmane, Nina N.; **397**
Hosseinipour, Mina C.; 313, 851, 874
Houben, Rein M.; 816LB
Houston, James C.; 615
Hovden, Arnt-Ove; 352
Hove, Malene; **758**, **803**
Howard, Louisa; 683, 756
Hoxie, James A.; 327, 348
Hoy, Jennifer F.; 779, 733, 736, 779
Hraber, Peter T.; 108
Hruska, Matthew; 509
Hsaio, Marvin; 35
Hsiao, Nei-Yuan; **34**, 864, 864
Hsieh, Anthony; **306**
Hsieh, Evelyn; **790**
Hsieh, Yu-Hsiang; 98, **667**
Hsu, Denise C.; **752**, 812, 813
Hsu, Ricky; 434
Hsue, Priscilla; 475, 731, 752, 755, 757, 759
Hsue, Priscilla Y.; 760
Hsue, Priscilla; 784
Hu, Hanxian; 777
Hu, Shiu-Lok; 348, 433
Hu, Wei-Shau; 45
Hu, Xiaohong; 1052
Hu, Yiran; 691
Hu, Zonghui; 752
Huang, Billy; **534**, **534**
Huang, Emily; 1098
Huang, Hannah; 107
Huang, Jenny; 609
Huang, Lisa; 307
Huang, Liusheng; 513
Huang, Meei-Lee W.; 27
Huang, Renxia; 619
Huang, Shujie; 1096
Huang, Szu-Wei; **235**
Huang, Taoying; 100
Huang, Tzu-Jung; 1036
Huang, Wei; **121**, **696**
Huang, Xiaohua; 145
Huang, Yong; 295, 317, 899
Huang, Yunda; **352**
Hudgens, Michael G.; 33, 886, 909, 948
Hueppe, Dietrich; 646, 646
Huerga, Helena; 32, 153, **555**, **1014**, **1079**
Hughes, Eric; 687, 688
Hughes, james; 978LB
Hughes, Lindsay; 1063, 764, 1063
Hughes, Michael D.; 870
Hughes, Sean; 366
Hughes, Stephen H.; **21**, 105
Huibner, Sanja; 271
Hulgan, Todd; **460**, 461
Hull, Mark; 1055
Hullegie, Sebastiaan J.; **669**
Hullsiek, Katherine H.; 836, 838, 772, 836, 838
Humphreys, Keith; 1121
Hung, Chien-Ching; 608
Hunt, Gillian; 908
Hunt, Peter W.; **4**, 88, 295, 317, 318, 382, 556, 722, 763, **899**
Hunter, Eric; 54LB, 364, 1044
Hunyh, Katie; 645, 645
Huprikar, Shirish; 799
Hurst, Jacob; 111LB, 921
Husk, Adam; 350
Husnik, Marla E.; 1033
Hutchings, Nicholas; 480
Hutchinson, Angela B.; 613
Hwang, Carey; 114LB

– I –

Iannetta, Marco; 329
Ibanescu, Ruxandra-Ilinca; 251
Ignacio, Caroline; 259
Ihenachor, Ezinne; 136
Ikapule, Jonathan; 577
Ike, Ndidi; **100**
Ikilezi, Gloria; 617
Ilan, Rabiner; 477
Imaz, Arkaitz; 553
Imbiakha, Brian; 214
Imperiale, Daniele; 487
Inci, Fatih; 421LB
Inciarte, Alexy; 959, 959
Incontri, Arianna; 466
Ingiliz, Patrick; 670, **671**, 678, 679, 680
Ingle, Suzanne M.; **837**, 579, **837**
Ingsrisawang, Lily; 863, 863
Innes, Steve; **926**, **929**
Insogna, Karl; 790
Irahara, Yu; 590
Ireland, Laurie; 1054
Iribarren, Jose Antonio; 918
Irrinki, Alivelu; 417
Irungu, Elizabeth; 980
Irvin, Risha; 667
Irving, Risha; 1017
Ismail, Nasreen; 359
Ismail, Nazir; 92
Ita-Nagy, Fanny; **90**
Ive, Prudence; 337, 571, 1120
Ivy, Wade; **850**
Iyer, Shilpa; **44**
Izopet, Jacques; 146, 274
Izquierdo-Useros, Nuria; 283

– J –

Jackson, Akil; 86LB
Jackson, Patrick E.; **201**
Jackson, Tonyka; 1018
Jacobs, William R.; 948
Jacobson, Denise L.; 801, **931**
Jacobson, Ira M.; 644, 644
Jacobson, Ira; 687
Jacobson, Jeffrey M.; 112LB, **402**
Jacobson, Lisa P.; 726, 489, 726, 743, 786, 797
Jacobson, Mark; 716
Jadlowsky, Julie; 402
Jagodzinski, Linda L.; 438
Jain, Mukesh K.; 298LB
Jain, Prashant; **40**
Jain, Vivek; 740, **1071**
Jakobsen, Martin; 123-A
Jakubowski, Aleksandra; 1056
Jamieson, Denise J.; 33, 868, 909
Janes, Holly; 51
Jani, Ilesh V.; 615
Janoff, Edward N.; 834, 815, 834
Janoff, Jordan; 834, 834
Janse van Rensburg, Anita; 912
Jao, Jennifer; **880**
Jaoko, Walter; 861, 853, 861
Jaquet, Antoine; **807**
Jarjour, Jordan; 401
Jarne, Ana; 337
Jarrin, Inma; **572**
Jaspan, Heather; 897
Jaumdally, Shameem Z.; **314**
Jaumdally, Shameem; 857
Javanbakht, Marjan; 672
Jaworowski, Anthony; 320
Jayathilake, Karu; 833
Jean Juste, Marc Antoine; 546
Jean_Louis, Reginald; 875
Jean-Philipe, Patrick; 36, 939
Jeffrey, Jerry; 327, **538**
Jenabian, Mohammad-Ali; 534, 534
Jenkins, Cathy; 833
Jennings, Kristofer R.; 61
Jensen, Kara; **948**
Jensen, Stig; 311
Jensen, Tomas O.; 628
Jere, Haswell; 879
Jerome, Keith R.; **400**
Jeste, Dilip; 484
Jia, Manxue; **344**
Jia, Xiaofei; 228
Jiamsakul, Awachana; 557
Jiang, Hongyu; 451
Jiang, Li; 216
Jiang, Wei; **342**
Jiang, Ying; 137, 745, 771
Jimenez de Ory, Santiago; 918, 942, 950
Jiménez de Ory, Santiago; 937
Jiménez-Sousa, Maria Ángeles; 682
Jimmerson, Leah C.; **518**
Jin, Fengyi; 1019LB
Jin, Hua; 56, 444
Jing, Jing; 736
Jing, Yuezhou; 726, 638, 726
Johansen, Isik S.; 877
John, Malcolm; 716
John-Stewart, Grace; 162, 866, 866, 884, 911, 1081
Johns, Brian; 538
Johnson, Brent; 1074
Johnson, Elan S.; 898
Johnson, Erica L.; **898**
Johnson, Gregory; 658, 668
Johnson, Jarrod S.; 46LB
Johnson, Jeffery A.; 120
Johnson, Margaret; 335, 377, 560
Johnson, Michael; 1114, 1114
Johnson, Oyigboja; 533, 533
Johnson, Phil; **66**
Johnson, Tory; 505
Johnson, Warren; 156
Johnston, Christine M.; 27
Johnston, Harvey E.; 409
Jolliffe, Darren; 352
Jonat, Brian; 843
Jones, Deborah L.; 273
Jones, Heidi E.; 857
Jones, Martin; 91
Jones, Rachael; 794, 798
Jones, Sarah; 653
Jones, Simon; 505
Jones, Trudy; 479, 840
Joos, Beda; 218
Jooste, Pieter; 921
Jordan, Andrea P.; 348
Jordan, Parris; 263
Joseph, Gregory; 506
Joseph, Jocelin; 376
Joseph, Sarah B.; 221, 439, **440**, 445
Joshi, Samit R.; 545
Joska, John A.; **455**
Jou, Toni; 414
Joulié, Aline; 650
Jourdain, Gonzague; 863, 511, 788, 831, 863
Joy, Jeffrey B.; 598, **697**
Joyce, M Patricia; **1027**
Judd, Ali; 913
Judge, Timothy; 521

Jumes, Patricia; 522
June, Carl H.; 402
Junker, Brian; 493, 494
Justice, Amy; 726, 837, 746, 467, 656, 726, 746, 837, 1049
Justman, Jessica E.; 1013

– K –

Kaaya, Sylvia; 809
Kabami, Jane; 1071, 1101
Kabudula, Chodziwadziwa; 161
Kaczmarek, Dominik J.; **680**
Kadakia, Nishi; 481
Kadar, Hanane; 138
Kadede, Kevin; 1101
Kagaayi, Joseph; 28, **1088**, **1088**
Kagihara, Jamie M.; 754
Kahle, Erin M.; 973
Kahn, James G.; 1056
Kahn, Kathleen; 825
Kaida, Angela; 899
Kaimila, Wongani; 719
Kaiser, Philipp; 210
Kaiser, Rolf; 431, 594
Kaja, Murali-Krishna; 898
Kajubi, Richard; 513
Kakaire, Tom; 1067
Kakkar, Fatima; 881
Kakuru, Abel; 513, 883
Kalams, Spyros; 900
Kalanga, Noel; 721
Kalapus, S. C.; 752
Kaleebu, Pontiano; 1038
Kaliballa, Sarah; 321
Kalish, Marcia L.; 236
Kallas, Esper G.; 318
Kallianpur, Asha R.; 460, **461**
Kallianpur, Kalpana J.; 754
Kalmin, Mariah M.; 660
Kamali, Anatoli; 94, 1044
Kamarulzaman, Adeeba; 820
Kamb, Mary; 1032
Kambo, Jaspreet; 598
Kambugu, Andrew D.; **57**, 88, 834, 119, 457, 552, 834, 1072
Kamiru, Harrison; 155, 938
Kammerer, Betsy L.; 936
Kampani, Coxcilly; 719
Kamwendo, Deborah; 909
Kamya, Moses R.; 740, 883, 887, 1056, 1071, 1101
Kamya, Philomena; 359
Kandathil, Abraham J.; **380**
Kandel, Gabor; 271
Kang, Guobin; 324
Kanki, Phyllis; 940, 1075
Kanters, Steve; 157, 1109
Kanthula, Ruth; 983
Kantor, Rami; 597, 619
Kanyama, Cecilia; 567
Kapetanovick, Suad; 468, 485
Kaplan, Jon; 573
Kaplan, Richard; 545, 1080
Kaplan, Robert C.; 729
Kapogiannis, Bill; 450
Kapoor, Sunaina; 1108
Karakas, Aram; 697
Karat, Aaron; **825**
Karchava, Marika; **664**
Kardava, Lela; 340
Karim, Farina; 830
Karim, Quarraisha Abdool; 622, 622, 987
Kariminia, Azar; 915
Karita, Etienne; 1044
Kariuki, Nyambura; 889
Karlsson, Elizabeth; 700
Karmon, Sharon L.; **305**
Karn, Jonathan; 404
Karnets, Iryna; 1042
Karris, Maile; 263
Karstaedt, Alan; 823
Kashuba, Angela; 548
Kasirye, Ronnie; 94
Kasolo, Josephine; 817
Kasper, Ken; 1054
Kassanjee, Reshma; 626, 626
Kastrati, Adnan; 730
Katabira, Elly; 24, 292, 1106
Katki, Hormuzd A.; 725, 725
Katlama, Christine; 139, 564
Kattakuzhy, Sarah; 653, 694, 695
Kattan, Meyer; 801
Katunguka, Edison; 573
Katz, David A.; 1061, 1061, **1093**, 1099
Katz, Ingrid T.; **1080**
Katzenstein, Terese L.; 877
Kaufman, Jonathan; 932
Kaul, Marcus; 481
Kaul, Rupert; 271, 1085
Kaur, Jasmine; 417
Kavanagh, Eoin; 774
Kawooya, Sulaiman; 577
Kayembe, Mukendi; 718
Kayira, Dumbani; 868
Kayuni, Ndoliwe; 1046
Ke, Ruian; 690
Kearney, Mary; 593
Kearney, Mary F.; **106**, 378
Kearney, Mary; 420, 593
Keating, Sheila; 626, 319, 626
Kebaya, Lilian M.; **889**
Keck, James W.; 721
Keele, Brandon F.; 286, 349, 378, 965
Keiser, Olivia; 150, 563, 675
Kekitiinwa, Adeodata; 941, **955**
Kelen, Gabor; **98**, 667
Keller, Marla J.; **992LB**
Kelley, Colleen F.; **973**
Kelly, Cliff; 982
Kelly, Erin M.; 639
Kelly, Paul; 762
Kelly, Sean G.; **743**
Kembabazi, Annet; 317, 899
Kemboi, Emmanuel; 597
Kendall, Michelle; 824
Kengne, Andre P.; 604
Kenney, Shannon C.; **69**
Kenny, Julia M.; **37**, **927**
Kent, Stephen; 363
Kerani, Roxanne; 1099
Kern, David; 1099
Kern, Winfried; 381
Kerr, Becky; 525
Kerr, Stephen J.; 703, 943, 956
Kersh, Ellen; **862**, 962, 963
Keruly, Jeanne; 101
Keshinro, Babajide; 764
Kessing, Cari; 413
Kessler, Benedikt M.; 169
Ketner, Elizabeth; 975
KewalRamani, Vineet; **125**
Keynan, Yoav; 1054
Kfutwah, Anfumbom; 230, 233
Khaitan, Alka; **278**
Khalilieh, Sauzanne G.; 521
Khamadi, Samoel; 459
Khan, Iram; 401
Khan, Nealia; 876
Khan, Palwasha Y.; 816LB, **885**
Kharfen, Michael; 854
Khasimwa, Brian; 1035
Khatib, Nadia; 794
Khoo, Saye; 86LB, 532, 533, 532, 533
Khosropour, Christine M.; **1061**, **1061**
Khouri, Ricardo; **338**
Khoury, Georges; **412**
Khromova, Irina; 637
Khurana, Nidhi; 1107
Kiani, Zahra; **277**
Kiarie, James N.; 861, 866, 861, 866, 980, 981, 1081
Kibbie, Jon; **262**
Kiconco, Sylvia; 513
Kidoguchi, Lara; 24, 969
Kidola, Jeremiah; 762
Kiem, Hans-Peter; 401, 433
Kiertiburanakul, Sasisopin; 557
Kiggundu, Reuben; 836, 826, 836
Kigozi, Godfrey; 30, 1084, 1088, 158, 1084, 1085, 1088
Kigozi, Joanita; 573
Kijewski, Suzanne D.; **222**
Kilama, Bonita K.; 570, **1076**
Kilby, J. Michael; 342
Kilembe, William; 54LB, 1044
Kim, Andrea A.; 625, **624**, 625
Kim, Arthur Y.; **14**, **16**
Kim, Baek; 207
Kim, Connie J.; **271**
Kim, Eunyoung; 288
Kim, Jerome H.; 51, 55LB, 166, 170LB, 272
Kim, Jim; 667
Kim, Kyeong-Ae; 208
Kim, Nina; 638
Kim, Peggy; 210
Kim, Stephanie; 508
Kincer, Laura; 221, 440
King, Caroline C.; **33**
Kingcade, Alvin; 645, 645
Kingsley, Lawrence; 463, 490, 506, 743, 786
Kinley, Bruce; 137, 738, 745, 925
Kinloch, Sabine I.; **335**, **377**
Kinuthia, John; 866, 866
Kiptiness, Catherine; 1081
Kiragga, Agnes N.; 573
Kirby, Karen; 585
Kirchhoff, Frank; 208
Kirk, Greg D.; 217, 638
Kirk, Gregory D.; 498, 623, 673, 783, 1053
Kirk, Ole; 142, 561, 739, 1094
Kirkpatrick, Allison R.; **623**
Kirmse, Brian; 880
Kirubi, Beatrice; 32, 153, 625, 624, 625, 1079
Kiser, Jennifer J.; 81, 518
Kiser, Patrick F.; 992LB
Kitahata, Mari M.; 748, 250
Kitahata, Mari; 638
Kitahata, Mari M.; 748
Kitahata, Mari; 749LB, 996, 1005
Kitandwe, Paul K.; 1038
Kitrinos, Kathryn M.; 530
Kittimunkong, Somyot; 971
Kityo, Cissy M.; 118
Kityo, Cissy; 119
Kityo, Cissy M.; 552, 557, 574, **595**
Kiwanuka, Noah; **1038**
Kiweewa, Francis; 459, 764
Kiyingi, Herbert S.; 1039
Kizito, Hilda; 953
Kjær, Anne Sofie; 405
Klamar, Cynitha; 389LB
Klarlund Pedersen, Bente; 803
Klatt, Nichole R.; 286
Klausner, Jeffrey D.; 1098
Kleerup, Eric; 490
Klein, Brandon; 525, 526
Klein, Daniel B.; 748, 748
Klein, Katja; **215**
Klein, Marina B.; **638**
Klein, Nigel J.; 35, 37, 919, 927
Kleinbeck, Kyle; 968
Kleiner, David; 708LB
Klevens, Monina; **145**
Klimkait, Thomas; 244, 245, 336
Klinbuayaem, Virat; 511
Kline, Tracy L.; 852
Klingman, Karin; 769LB
Knibbe, Jaclyn; 543
kniesch, Katja; 297
Knight, Vijaya; 312
Knudsen, Troels Bygum; **316**
Ko, Nerissa; 760
Kober, Kord; 294
Koblin, Beryl A.; 116, 1017
Kodama, Eiichi; 585
Koekkoek, Kristine; 243
Koelsch, Kersten; 437
Koelsch, Kersten K.; 761, 1019LB
Koenig, Ellen; 143LB
Koenig, Helen C.; 975
Koenig, Noshin; 471
Koenig, Serena P.; 1012
Koethe, John; **762**
Koh, Christopher; **708LB**
Kohgo, Satoru; 537
Kohler, Philipp; 1008
Kohli, Anita; 148, 653, 683, 689, 694, 695
Kohli, Payal; **731**
Kohrt, Wendy; 859, 859
Kojic, Erna; 713
Kok, Yik Lim; **199**
Kokordelis, Pavlos; **678**, 680
Kolawole, Grace; 1075
Kolson, Dennis L.; 61, 501, 502
Kolte, Lillian; 758
Kong, Rui; **346**
Kong, Xiangrong; 1088, **158**, 452, 453, 454, 458, 1088
Kongpechsatit, Oranuch; 1026

Kooij, Katherine W.; **806**
Koole, Olivier; 885, 1046
Koontz, Dianna; 379, 379, 398
Koopmans, Peter P.; 669
Kootstra, Neeltje; 381, 806
Kopp, Jeffrey; 933
Korber, Bette; 346
Kordelas, Lambros; 431
Korenromp, Eline; 832
Kosakovsky Pond, Sergei L.; 58, 239, 240, 246, 259, 435, 492
Kosalaraksa, Pope; 956
Koshuma, Sifuni; 1086, 1086
Koss, Catherine A.; **887**
Kostadinova, Lenche; **684**
Kostman, Jay R.; **645**, 376, **645**, 656
Kotler, Donald; 647
Kottilil, Shyam; 148, 653, 681, 683, 689, 692, 694
Kottilil, Shyamasundaran; 695
Kotwani, Prashant; 740
Kouame, Gerard M.; 115LB
Koulla-Shiro, Sinata; 782, 782, 793
Koumans, Emilia; 615
Kouokam, J. Calvin; 350
Koup, Richard A.; 49, 50, 167, 394
Kouri, Vivian; 338
Kourtis, Athena P.; 33, 868, 886, 909
Kouyos, Roger; 150, 199, 244, 245, 253, 675
Kovacs, Colin; 271, 448, 465, 467
Kovacs, Joseph A.; 520, 928
Kovari, Helen; **805**
Kowadisaiburana, Boonchai; 957, 957
Kowalski, John P.; 401
Kpamou, Cece; 1077
Kraeusslich, Hans-Georg; 381
Krajden, Mel; 697
Krakower, Douglas S.; 972, **1083**
Krämer, Benjamin; 678, **679**, 680
Kravietz, Adam; 278
Krebs, Shelly J.; **170LB**, 438
Kreider, Edward; **169**
Kreitchmann, Regis; 894
Krishnan, Sonya; 302, 302
Krishnan, Supriya; **763**
Kristoff, Jan; 268
Kroetz, Deanna; 295
Krogan, Nevan; **171**
Kroidl, Arne; **544**
Kronborg, Gitte; 316
Kroon, Eugene; 272, 438, 841
Kroon, Max; 34
Kruglov, Yuri; 1042
Krysiak, Robert; 719
Krystal, Mark; 114LB, 539
Krznaric, Ivanka; 671
Ku, Lawrence; 648, 648
Kubo, Michiaki; 295
Kucherer, Claudia; 602
Kuehnert, Denise; 247
Kuhar, David; 1027
Kuhn, Louise; 908, 910, 930, 932
Kuijpers, Taco W.; 935
Kulich, Michal; 629
Kumar, Muniratnam S.; 1016
Kumar, Nitasha A.; 388
Kumar, Parag; 520
Kumar, Sonal; 644, 644
Kumarasamy, Nagalingeswaran; 313
Kumwenda, Johnstone; 1047
Kumwenda, Newton; 869
Kumwenda, Newton I.; 1047
Kuniholm, Mark; 676
Kuniholm, Mark H.; 1050
Kunz, Erika; 903
Kuo, Alex; 661
Kuo, Irene; **665**
Kuritzkes, Daniel; 110LB, 235, 307, 421LB
Kuritzkes, Daniel R.; 430
Kurland, Irwin; 880
Kurniati, Nia; 956
Kurt Yilmaz, Nese; 693
Kurth, Ann; 1095
Kuruc, JoAnn D.; 1003
Kusiima, Joy; 1039
Kuster, Herbert; 199, 218
Kutscher, Hilliard L.; **542**
Kuwata, Takeo; 589
Kwakwa, Helena; **1078**
Kwarisiima, Dalsone; **740**, 1071, 1101
Kwiatkowski, Robert; 91
Kwobah, Charles; 57
Kwok, Justin; 1098
Kwong, Peter D.; 170LB

– L –

La Mar, Melissa; 305, 446
La Rosa, Alberto; 107
Laanani, Moussa; **373**
Labbato, Danielle; 137, 745, 925
LaBranch, Celia; 904
LaBranche, Celia; 221
Lacabaratz, Christine; 353, **819**
Lacey, Simon; 402
Lachenal, Guillaume; 230
Lachowsky, Nathan J.; 1023, **1024**, **1025**
Lacombe, Karine; 146, 637, 706
Lada, Steven; 376
Laeyendecker, Oliver B.; 98, **622**, 217, **622**, 623, 667, 673, **987**
Laga, Marie; **72**
Lago, Lena; 854
Lai, Ming-tain; 449
Laird, Greg; 427, 427
Laird, Gregory M.; **419**
Laird, Melissa; 259
Lake, Jordan; 786
Laker-Oketta, Miriam O.; 88, 722
Lal, Allan; 1025
Lal, Asim A.; 898
Lala, Sanjay; 872
Lalani, Tahaniyat; 847
Lalezari, Jay; 147, 417, 434, 545, 688
Lallemant, Marc G.; 863, 863
Lalley-Chareczko, Linden; 975
Lalloo, David; 835, 835
Lam, Linda; 320
Lam, Stephen; 802
Lam, Wan; 802
Lama, Javier R.; 778
Lama, Javier; 567
Lama, Javier R.; 778
Lambers, Femke A.; 674
Lambert, Caroline; 237
Lambert, John S.; 732
Lambotte, Olivier; 52, 333
Lamorde, Mohammed; 85LB
Lampe, Fiona; 560
Lampiris, Harry; 210
Lancaster, Kathryn E.; **851**
Lancaster, Kathryn; 874
Landais, Elise; 259
Landay, Alan; 268, 320, 358, 486, 763, 1050
Landolfi, Stefania; 714
Landovitz, Raphael J.; **20**, 515, 716
Lane, H. Clifford; **77**
Langat, Rither; 459
Langer, Robert; 357
Langness, Jacob A.; 81, 518, **652**
Langwenya, Nontokozo; 857
Lansky, Amy; 1040, 1115
Laopraynak, Naphassanant; 841
Lapadula, Giuseppe; 466
Lapasset, Laure; 104LB
Lariven, Sylvie; 891
Larsen, Ellen M.; **877**
Larsen, Michelle H.; 948
Larsson, Marie; 820
Lascoux-Combe, Caroline; 706
Lassmann, Hans; 814
Lataillade, Max; **114LB**, 545
Lattimore, Sam; **662**
Lau, Bryan; 996
Laufs, Stephanie; 381
Laughton, Barbara; 912, 926
Laugwitz, Karl-Ludwig; 730
Laumann, Edward; 1070
Launay, Odile; 329, 701
Laut, Kamilla G.; **561**
Lauw, Fanny N.; 669, 674
Lavandier, Nora; 921
Lavocat, Fabien; 706
Law, Matthew G.; 315
Law, Matthew; 582
Law, Matthew G.; 805
Lawler, Leo P.; 732
Lawson, Eileen; 953
Lawton, Mark D.; 961, 961
Lawyer, Glenn; 229
Lazzarin, Adriano; 442, 443, 773
Le, Binh; 1060, 1060
Le, Thoa P.; 943
Le, Thuy; **843**
Le Carrou, Jerome; 115LB
Le Chenadec, Jérome; 867
Le Coeur, Sophie; 863, 863
Le Moing, Vincent; 727, 727, 793
Le Rouzic, Erwann; 540
Leaf, David; 1049
Leal, Lorna; **959**, **959**, 960
Leal, Manuel; 167
Lebaron, Charles; 632LB
Lebbink, Robert Jan; 403
Lecci, Fabrizio; 493, 494
Lechenadec, Jerome; 334
Lecher, Shirley; 1082
LeCiel, Cosette; 897
Lecuroux, Camille; 333
Ledergerber, Bruno; 805, 1008
lederman, michael; 298LB
Lederman, Michael M; 308, 337, 738, 763
Ledwaba, Johanna; **908**
Lee, Anthony; 716
Lee, Caroline S.; 426
Lee, Chih-Hao; 235
Lee, Eric; 186, 262
Lee, Eunok; 382
Lee, Fang-Hua; 349
Lee, Frederick J.; **733**
Lee, Gary; 434
Lee, Guinevere Q.; 633
Lee, Ha Youn; **254**, **254**
Lee, Hana; 1073
Lee, Samuel; **687**
Lee, Sook-Kyung; 42
Lee, Sulggi A.; **295**, **317**, 428LB
Lee, Vincent; 798
Lee, Wingyiu; **189**
Leelawiwat, Wanna; 635, 855, 986
Leenasirimakul, Prattana; 511
Leethochawalit, Manoj; 971
Leff, Jared A.; 1113
Lehman, Dara A.; 983
Lei, Quanhong; 876
Leidner, Jean; 870, 871
Leigh Brown, Andrew J.; 236, 249, 253
Leisegang, Rory F.; 604
Leister, Erin; 801, 882
Leitman, Ellen M.; **362**
Lelièvre, Jean-Daniel; 206, 819
Lemee, Veronique; 230, 232
Leng, Sean X.; 783
Lennemann, Tessa; 544
Lennox, Jeffrey L.; 515
Leon, Agathe; 959, 354, 959, 960
Leon, Ngeruka; 1087, 1087
León-Leal, Juan Antonio; 950
Leone, Dominick; 1080
Leone, Sebastiano; 466, **655**
Leong, Yew Ann; **358**
Leoz, Marie; **230**
Lerdlum, Sukalaya; 438
LeRoith, Derek; 880
Lerolle, Nathalie; 333
Leroy, Valeriane; 512
Lesko, Catherine R.; **578**
Letai, Anthony; 411
Letendre, Scott; **56**, 58, 435, **436**, 444, 460, 461, 462, 469, 474, 478, 483, 484, 491, 492, 497
Leth, Steffen; 369
Letlhogile, Rona; 810
Leuenberger, David; **103LB**
Leung, Janice M.; **802**
Leurgans, Sue; 486
Leuvennink, Mildie; 995
Levendosky, Keith; 967, 968
Levi, José Eduardo; 856
Levin, Carol; 1111, 1111
Levin, Jonathan B.; **94**
Levin, Myron; 917
Levin, Simon; 89
Levine, Andrew; 463, **464**, 493
Levine, Bruce; 402
Levine, Calley; 647
Levine, Kenneth; 972
Levy, Claire; 366
Levy, David N; **426**
Levy, Jeremy; 794, 798
Lévy, Yves; 206, 337, 353, 819

Lewin, Sharon R.; 109, 281, 358, 388, 428LB
Lewis, Mark; 324
Lewis, Martha J.; 226
Lewis, Rashunda; 1031
Lewis, Robert; 661
Li, Chun; 360, 517
Li, Duo; **207**
Li, Eric; 686
Li, Fang-yong; 62
Li, Feng; 677
Li, Guangming; 677
Li, Hui; 169, 406
Li, Jia; 197
Li, Jonathan; **110LB**
Li, Jonathan Z.; **378**
Li, Kevin; 299LB
Li, Ming; 416
Li, Peilin; **210**
Li, Qingsheng; 324
Li, Taisheng; 790
Li, Tiandong; 450
Li, Xiao-Dong; 310
Li, Xiuhong; 743, 786
Li, Yingying; 44
Li, Yue; 324
Li, Yuxing; 340
Li, Zehang; 583
Li, Zhe; **585**
Liang, Feng-Xia; 46LB
Liang, Richard; 592
Liao, Hua-Xin; 905
Libertone, Raffaella; 63
Liberty, Afaaf; 930
Libin, Pieter; 610
Liblau, Roland; 814
Libre, Camille; **193**
Lichlyter, Philip; 183
Lichtenstein, Kenneth A.; 747, **312**, 747, 772, 795
Lichterfeld, Mathias; 53, 185, 360, 369, 405
Lichtner, Miriam; 303, 303
Liebenberg, Lenine; 314
Liegler, Teri; 209, 386
Lifson, Jeff; 428LB
Lifson, Jeffrey; 168
Lim, Joseph K.; 656
Lim, So-Yon; 108
Limiti, Silio; 495
Limou, Sophie; **197**
Lin, Hazel; 395
Lin, Jue; 784
Lin, Kuan-Hung; **586**
Lin, Nina; 307
Lin, Sonia; 652
Lin, Wendy; 46LB
Lin, Zeyu; 539
Lindegaard, Birgitte; 803
Linder, Grace; 826
Lindsey, Jane; 36, 939
Lingappa, Jairam R.; 290, 292
Linley, Laurie; **1043**
Liomba, George; 719
Liotta, Giuseppe; 879
Lippincott, Christopher; 439, 445
Lipshultz, Steven E.; 882
Liptrott, Neill; 519
Lisco, Andrea; 304, 304
Lisinicchia, Joshua G.; 61
Little, Susan; 240, 246, 263, 288
Little, Susan J.; 375
Little, Susan; 600
Little, Susan J.; 1020
Little, Susan; 1021
Little, Susan J.; 1022
Littman, Dan R.; 46LB
Liu, Albert; 25, 514, 970, 1017
Liu, Chia-Ying; 756
Liu, Cindy M.; **1085**
Liu, Enju; 606
Liu, Fengying; 1096
Liu, Haichuan; 208
Liu, Hongjie; 1063, **1030**, 1063
Liu, Joseph C.; 802
Liu, Karen; 979
Liu, Lin; **686**
Liu, Rachael; 521
Liu, Tao; **619**
Liu, Xia; 444
Liu, Xin-Ming; 528, 529
Liu, Ya-Pei; 954
Liu, Yang; 530
Liu, Yiying; 744
Liu, Yutong; 504
Liu, Zhaohui; 151LB
Liu, Zheng; 539
Liu, Ziyue; 737
Livak, Britt; 319
Livelli, Alessandro; 487
Llach, Josep; 960
Llibre, Josep M.; **553**
Lo, Janet; **136**, 138
Lo, Nathan C.; **160**
Lo Re, Vincent; 645, 638, 645, **656**
Lobritz, Mike; 215
Lockett, Stephen; 45
Lockhart, Ainsley; 307
Lockman, Shahin; 630, 711, 718, 870, 878
Lohman-Payne, Barbara; 1035
Loiseau, Claire; **274**
Lombard, Carl; 26LB
Long, Lawrence; 781, 571, 781, 1091, 1120
Longenecker, Chris T.; 137, **744**
Longenecker, Christopher T.; 925
Longo, Valeria; 443
Longosz, Andrew F.; 622, 622
Longosz, Andrew; 869, 987
Looby, Sara; 136
López, Juan Carlos; 657
Lopez-Galíndez, Cecilio; 347
Lorenzana, Ivette; 601, 607
Lorenzini, Patrizia; 63
Loring, David W.; 440
Losina, Elena; 93, 1104, 1119, 1015, 1104, 1119
Losso, Marcelo H.; 315
Louder, Mark; 346
Louie, Aaron; 340
Loulergue, Pierre; 329
Love, Tanzy; 254, 254
Low, Hui Zhi; **282**, 297
Lowe, Anita; 160
Lowry, Anabel; 966LB
Lu, Lydia; **875**
Lu, Michael; 136
Lu, Wuxun; **324**
Lu, Wuyan; 211
Lubanga, Augustine; 577
Lubin, Susan; 523
Lübke, Nadine; 431
Lucas, Gregory M.; 1016
Lucera, Mark B.; **404**
Lucero, Constanza; 959, 959
Luciw, Paul; 535, 535
Luechai, Pikunchai; 1026
Luetkemeyer, Anne; 151LB, **824**
Lugemwa, Abbas; 457
Lum, Garret; 29, 854
Lumbiganon, Pagakrong; 915
Lumeng, Carey; 763
Lund, Jennifer; 290
Lundgren, Jens D.; 142, 561, 582, 637, 739, 742, 761, 805
Lundgren, Louise; **695**
Lunding, Suzanne; 877
Lungu, Thandie; 710, 851
Luo, Wei; 620
Luo, Zhenwu; 342
Lupo, L Davis; 860, 860
Lurain, Nell; 319
Lurie, Mark; 1116
Lurton, Gregoire; 584
Lutaakome, Joseph; 941
Lutalo, Tom; 1036
Lutgen, Victoria; **507**
Luton, Dominique; 1122
Lutung Amor, Penninah; 577
Lutz, Thomas; 646, 646, 670
Luz, Paula M.; **1119**, 856, **1119**
Luzuriaga, Katherine; 374, 396
Lycett, Samantha; 249
Lynn, Kenneth; 645, 645
Lyons, Claire E.; 476
Lyons, Jennifer; 455

– M –

M. Souza, Thiago; 190
Ma, Dongzhu; 406, 965
Ma, Fangrui; 324
Ma, Qing; 436, **444**
Ma, Yifei; 731, 755, 757, 770, 784
Ma, Zhing-Min; 548
Ma, Zhong-Min; 267, 270, 547
Maan, Evelyn; 901
Maartens, Gary; 559, 604
Mabileau, Guillaume; **1122**
MacArthur, Rodger D.; 315
Macatangay, Bernard J.; **389LB**
Mackay, Charles; 358
Mackelprang, Romel D.; **292**, 1035
Macken, Alan; 732, 774
Mackenzie, Charlene; 412
Mackie, Nickie; 961, 961
Macleod, William; 154
MacPherson, Peter; 634
Madlala, Paradise; 198
Maeda, Kenji; **537**
Maestre, Ana; 187
Magaldi, Lora; 658, 668
Maganga, Lucas; 544, 764
Magaret, Amalia S.; 27
Magaret, Amalia; 945
Maggiolo, Franco; 655
Magiorkinis, Gkikas; 229
Magnus, Carsten; 39, 165
Magnus, Manya; 1017
Magogotya, Zukiswa; 926
Mahajan, Garima; 350
Mahajan, Sandeep; 666
Mahapatra, Sebabratra; 309
Maharaj, Shavani; 604
Mahiti, Macdonald; 227, 228
Mahle Gray, Kristen; 1043
Mahler, Hally; 1086, 1086
Mahomed, Kay; 781, 781
Mahon, Niall G.; 732
Mahy, Mary; 1118
Maillard, Anne; 232
Majoie, Charles B.; 935
Majola, Nelisile; 984
Maka, Kristinalisa; 731, 752, 757, 759
Makanani, Bonus; 31LB
Makarov, Edward; 504
Makarova, Natalia; 963
Makhema, Joseph; 630, 871, 876, 878, 990
Makinson, Alain; **727**, **727**
Makita, Faithful; 542
Makombe, Simon; 634
Makumbi, Fred; 28
Malatinkova, Eva; 377, 424
Maldarelli, Frank; 105, 399, 420
Maleche-Obimbo, Elizabeth; 800, 911
Malee, Kathleen M.; 936
Malema, Owen; 634
Malete, Given; 1091
Mallolas, Josep; 959, 959
Mallon, Patrick W.; 779, 732, 774, 779
Malvy, Denis; 103-ALB
Malyuta, Ruslan; 1042
Mamais, Ioannis; 229
Maman, David; **32**, **153**, 625, 555, 624, 625, 1014, 1079, **1090**
Man, S. F. Paul; 802
Manabe, Yuka; 815
Manabe, Yukari; 573
Manasa, Justen; 256, 248, 256, 603
Mancinelli, Sandro; 879
Mandal, Sema; 662
Mandelbrot, Laurent; 867, 1122
Manel, Nicolas; 46LB, **184**, **184**
Manga, Nestor; 793
Mangal, Tara D.; **97**
Mangalasir, Parana Hewage; 1089, 1089
Manganaro, Lara; **187**
Mangat, Sabrina; 683, 756
Mangioni, Davide; 466
Manier, Celine; 819
Manion, Maura M.; 311
Mankowski, Joseph L.; 476
Mankowski, Madeleine; 685
Mann, Marita; **712**
Mann, Surinder; 547, 548
Mannathoko, Naledi; 846
Manosuthi, Weerawat; 957, 957
Manousopoulou, Antigoni; 409
Mantell, Joanne E.; 1103
Manthos, Helen; 521
Manucci, Jordyn L.; **30**, 1084, 98, 1084
Manuzak, Jennifer; **329**
Manzanero, Marvin; 242, 601
Manzardo, Christian; 837, 640, 837

Mao, Lu; 89
Maponga, Charles C.; 542
Marazzi, Maria Cristina; 879
Marc, Pellegrini; 358
Marcelin, Anne-Genevieve; 564, 594
Marchand, Bruno; 585
Marchetti, Giulia; 303, 303, 705
Marchou, Bruno; 274, 814
Marconi, Vincent C.; 746, 746, 1074
Marcotte, Thomas; 474, 497
Marenco, Ted; 522
Margolick, Joseph B.; 786, 797
Margolis, David; 372
Margolis, David A.; **554LB**
Margolis, Jessica; 445
Marinaro, Letizia; 487, **791**
Maritz, Jean; 616
Markowitz, Lauri E.; 842, 855
Markowitz, Martin; 305, 446
Marks, Gary; 101
Marks, Kristen M.; **644**, **644**
Marlin, Robert; 1098
Marlink, Richard; 990
Marmorino, Jenni; 1003, 1018
Maroa, Jenniffer K.; **339**
Marquet, Roland; 193
Marra, Christina; 451, 479, 483, **840**
Marrazzo, Jeanne M.; 27
Marrazzo, Jeanne; 979, 982
Marshall, Brandon; 1116
Marshed, Fatma; 278
Marson, Kara; 626, 209, 626
Marston, Barbara; 875
Marston, Milly; 1046
MARTI, RAMON; 196
Martí, Ramón; 204, 205
Martin, Alyssa R.; 427, **415**, 419, 427
Martin, Darren P.; 231
Martin, Edward; 365
Martin, Eileen; 463, 489, 493
Martin, Hal; 113LB
Martin, Jeffrey; **88**, 295, 317, 556
Martin, Jeffrey N.; 722
Martin, Jeffrey; 899
Martin, Lisa; 342
Martin, Michael T.; 635, **971**, 986
Martin, Philip; **527**
Martin-Blondel, Guillaume; **814**
Martin-Carpenter, Louise; 550
Martin-Gayo, Enrique; **185**
Martín-Nalda, Andrea; 934
Martinez, David R.; **904**
Martinez, Esteban; 733, 845
Martinez, Oto; 490
Martínez, Miguel Ángel; 587
Martinez-Dueñas, Loreto; 709
Martinez-Peinado, Antonio; 709
Martínez-Picado, Javier; 283, 414, 432, 594
Martinez-Pourcher, Valérie; **723**
Martinez-Rebollar, Maria; 959, 959
Martins, Laura J.; 424
Martins, Mauricio A.; 361
Martinson, Francis; 31LB
Martinson, Jeremy J.; 463
Martinson, Jeremy; **506**
Martinson, Neil; 822, 827LB
Martinson, Neil A.; 872
Martinson, Neil; 907
Martrus, Glòria; 587
Marty, Francisco M.; 430
Maruri, Fernanda; 900
Maruta, Yasuhiro; 589
Marzel, Alex; **244**, 245
Marzinke, Mark A.; 116, 629, 969, 988, 992LB, 994
Marzolini, Catia; **531**, **531**
Masaku, Dorica; 37, 927
Masaninga, Masumba; 808
Mascia, Claudia; 303, 303
Masciotra, Silvina; **620**
Mascola, John; 49, 50, 346
Masese, Linnet; 861, 853, 861
Mashabela, Fildah; 822, 872, 907
Masià, Mar; 553
Masiku, Charles; 32, 153, 1079, 1090
Maskew, Mhairi; 781, 571, 781, 1091, 1120
Masliah, Eliezer; 464, 481
Mason, Stephen; 371
Massanella, Marta; 300, 391, 300, **330**, **331**, 375, 391
Massaro, Joseph; 751, 751
Masson, Lindi; 314
Masson, Sophie; 1090
Masters, Samuel; 584
Masur, Henry; 148, 485, 660, 681, 683, 689, 692, 695
Masur, Jack; **694**
Maswai, Jonah; 764
Matano, Tetsuro; 590
Matemo, Daniel; 866, 866
Mateo, Gracia; 767
MATEOS, ELENA; 196
Mathema, Barun; 92
Matheron, Sophie; 891, 1122
Mathews, Christopher W.; 1005
Mathias, Anita; 82
Mathias, Augusto; 318
Mathur, Sanyukta; 1036
Matining, Roy; 710
Matoba, Nobuyuki; **350**
Matos de Silva, Carlos Adriano; 309
Matsen, Frederick; 983
Matsuda, Kenta; **503**
Matsui, Yusuke; 200
Matsuoka, Masao; 589
Matsushita, Shuzo; 589, 590
Matthews, Lynn T.; 899
Matthews, Paul; 477
Matthews, Philippa C.; 362
Matthews, Philippa; 896
Matthias, Torsten; 297
Mattson, Christine L.; 1057
Matyas, Robert J.; 754
Mauclere, Philippe; 230
Mauff, Katya; 559
Maugham, Geoffrey; 665
Maung, Ricky; 481
Maurer, Toby; 88
Mauss, Stefan; **646**, **646**, 670
Mavian, Carla N.; 183
Mavilio, Domenico; 367
MaWhinney, Samantha; 859, 859
Maxwell, Nicky; 724, 724
May, Margaret T.; 837, 576, **579**, 837
Mayanja, Faridah; 1067
Mayer, Kenneth H.; 116, 269, **972**, 996, 1005, 1017, 1083
Mayer, Kenneth; 1116
Maylin, Sarah; 706
Mayo, Nancy; 469
Mayor, Angel M.; 726, 580, 726
Mazurek, Gerald; 824
Mben, Jean-Marc; 782, 782
Mbidde, Edward; 88, 722
Mbondji, Christelle; 258, 258
Mbwambo, Jessie K.; 629
Mc Gowan, Catherine; 580
Mc Laren, David; 1089, 1089
McAllister, John; 958, 958
McAllister, Kevin; 526
McArthur, Carole; 234
McArthur, Justin; 455, 497
McCallister, Scott; 113LB
McCarter, Martin; 186, 262
McCarthy, Geraldine; 774
McCarthy, Kerrigan; 825
McClelland, R Scott; 861, 853, 861
McComsey, Grace A.; **137**, **140**, 738, 744, 745, 771, 925
McCormack, Sheena; **22LB**
McCormick, Tyler; 583
McCoy, Connor; 983
McCune, Joseph M.; 320
McCutchan, Allen; 483
McDanal, Charlene; 538
McDaniel, Darius; 1074
McDonald, Tom O.; 527
McElrath, M Juliana; 292
McFall, Allison M.; 641, 1016
McFarland, Elizabeth; 905, 951
McFarland, Willi; 1010
McGary, Colleen; 168
McGinnis, Kathleen; 50
McGovern, Barbara; 147, 691
McGovern, Mark; **1102**
McGowan, Catherine; 833
McGowan, Ian; 269, 993, **994**
McGregor, Donna V.; 649, 649
McGuire, Erin; 905
McHutchison, John; 148, 152LB
McIntyre, James A.; 864, 864, 888
McKay, Heather; 797
Mckinney, Elaine; 618
McKinney, Elaine; 626, 626
McKinstry, Laura; 1095, 1100
McKnight, Aine; **192**, **192**
McKnight, Áine; 332
McLaren, Paul J.; 291, **293**
McLaughlin, Milena M.; 649, 649
McLaughlin, Sherry; 107
McLean, Estelle; 583, 1046
McMahan, Vanessa; 970, 977
McMahon, Deborah A.; 389LB
McMahon, James H.; 428LB, 1011
McManus, Maryellen; 520
McMichael, Andrew J.; 169
McMillan, JoEllyn; 528, 529, 543
McNairy, Margaret L.; 156
McNerney, Ruth; 816LB
McNicholl, Janet; 510, 635, 855, 862, 962, 963, 986
McNulty, Anna; 958, 958
McShane, Helen; 818
Mdolo, Aaron; 634
Méa-Assande, Véronique; 512
Meassick, Elizabeth; 1039
Medhin, Heluf; 711, 718
Meditz, Amie; **859**, 83
Meditz, Amie L.; 525
Meditz, Amie; 526, **859**
Medline, Alexandra; **1098**
Medoeva, Antonia; 1042
Medvedovic, Mario; 698
Mefford, Joel; 295
Mehri, Zaher; 858, 858
Mehrotra, Megha; 970, 977
Mehta, Sanjay; 239, 240, 242, **246**, 496, 499, 600, 1020, 1021, 1022
Mehta, Shruti; 217
Mehta, Shruti H.; 498, 623, **641**, 673, 783, 1016
Meigs, James B.; 751, 734, 751
Meintjes, Graeme; 835, 604, 811, 835
Meissner, Eric; 518
Meissner, Eric G.; **681**
Mejía-Villatoro, Carlos; 242, 601
Melaku, Zenebe; 914
Melander, Kelsey; 859, 859
Mélard, Adeline; 373
Melbourne, Kathy; 738, 787
Melcher, Gregory; 270
Melekhin, Vlada; 900
Melica, Giovanna; 819
Melki, Marie-Thérèse; 285
Mellado, Maria Jose; 937
Mellins, Claude A.; 888
Mellors, John W.; 593, 379, 105, 106, 110LB, 371, 379, 389LB, 398, 420, 593, 912, 982, 985
Meloni, Seema; 1075
Menager, Mickael M.; **46LB**
Ménan, Hervé; 115LB
Mende, Katrin; 847
Mendoza, Maria; 1060, 1060
Mendrone, Alfredo; 1010
Menezes, Prema; 439, 440, 445
Menichetti, Samanta; 63
Menzaghi, Barbara; 765
Mercie, Patrick; **139**
Merlini, Esther; 303, 303, 705
Mermin, Jonathan; 1115
Merry, Concepta; 85LB
Mesani, Linda; 581
Mesplede, Thibault; 591
Mesquita, Pedro; 510, 992LB
Messou, Eugène; 576
Metz, Meghan; 402
Metzner, Karin J.; 255, 199, 218, 255
Mewalal, Nikoshia; 359
Meya, David B.; 834, 836, 838, 454, 573, **815**, 826, 834, 836, 838
Meyer, Laurence; 23LB, 146, 333, 373, 1051
Meyer-Olson, Dirk; 297
Meyerhoff, Dieter; 60
Meyerson, Nicholas; 223
Meza, Rita; 607
Mezzacappa, Catherine; 1062, 1028, 1062
Mezzaroma, Ivano; 296
Mgaya, Jimson; 544
Miailhes, Patrick; 701, 706

Micci, Luca; **168**
Michael, Denna; 583
Michael, Nelson L.; 47, 48, 50, 51, 166, 170LB, 841
Michael, Starnbach; 357
Michael, Yvonne; 890
Michaels, Stuart; 1006, 1070
Michel, Marie-Louise; 701
Michelow, Pam; 89
Mida, Jose M.; 827LB
Middel, Ananja; 549
Mielke, Michelle; 497
Mikre, Meriam; 665
Milani, Karine; 318
Milanini, Benedetta; **495**
Milazzo, Laura; 705
Miller, Andrew D.; 753
Miller, Caitlin; 222
Miller, Christopher; 267, 270, 547, 548
Miller, Elizabeth A.; 284
Miller, Eric; 489, 490, 494
Miller, Michael D.; **449**, 530, 605, 952
Miller, Scott C.; 536
Miller, Tracie L.; 931
Miller, William C.; 851, 886
Millet, Joan-Pau; 827LB
Milligan, Caitlin; **162**, **906**
Milligan, Michael G.; **718**
Milling, Jacob; 542
Mills, Claire; 760
Mills, Edward; **157**, 1109
Mimiaga, Matthew; 804, 972, 1005
Minemo, Junichi; 402
Minkoff, Howard; 792
Miralles, Pilar; 657
Miranda, Milene; 190
Mirani, Gayatri; **917**
Mirembe, Grace; 37, 927
Miro, Jose M.; 837, 837
Miro, Jose M; 640
Mirochnick, Mark; 892, **894**
Mirza, Ayesha; 954
Misra, Vikas; 498
Mitchell, Brenda; 1067
Mitchell, Brooks I.; 754, **796**
Mitchell, Caroline; 107
Mitchell, James; 962
Mitchnick, Mark; 992LB
Mitsuya, Hiroaki; 537, 585
Mitsuyasu, Ronald T.; 434
Miura, Toshiyuki; 227, 275, 276
Miyahara, Reiko; 275, 276
Miyaji, Karina T.; 318
Miyamasu, Misato; 281
Mlanga, Erick; 1086, 1086
Mlaudzi, Naledi M.; 990
Mlisana, Koleka; 92
Mmalane, Mompati; 871, 878
Mmbando, Donan; 570, 1076
Mncube, Busi; 829
Mocello, A. Rain; 88, 722
Mock, Philip; 971
Mocroft, Amanda; **142**, 561, 582, **637**, 742, 766
Moecklinghoff, Christiane; 551
Moesker, Bastiaan; **408**
Moestrup, Søren; 316
Mofenson, Lynne; 31LB, 36, 894, 920, 933, 939
Mofolo, Innocent; 874
Moh, Raoul; 115LB, 544
Mohamed, Mona; 482
Mohanakrishnan, Janardhanan; 704
Mohr, Erika; 829
Moir, Susan; 340
Moisi, Daniela; 251, 591
Molina, Jean-Michel; **23LB**, 113LB, 146
Mollan, Katie; 948
Molsberry, Samantha A.; 463, **493**, 494
Molteni, Chiara; 765
Moltó, José; 964
Momplaisir, Florence; 890
Money, Deborah; 881, 901
Mongwenyana, Constance; 1091
Monroe, Anne; **489**, **1065**
Montaner, Julio; 117, 157, 802, 1023, 1055
Montaner, Luis J.; 367, 376, 975
Montange, Thomas; 334
Montebello, Sandra; 1010
Montefiori, David; 221, 346, 904
Monteiro, Polyana; 733
Montezuma-Rusca, Jairo Mauricio; 340
Montgomery, Nathan; 719
Monus Arias, Isa; 202, 202
Moodley, Amber; 359
Moodley, Pravi; 92
Moore, David J.; 436, 464
Moore, David; 481
Moore, David J.; 483, 484
Moore, David; **1023**, 1024, 1025
Moore, Richard; 726, 1104
Moore, Richard D.; 748
Moore, Richard; 580
Moore, Richard D.; 623
Moore, Richard; 638, 726, 733
Moore, Richard D.; 748
Moore, Richard; 749LB, 1019LB, 1065, 1104
Moorthy, Ganesh; 975
Mora, Stefano; 765
Morales-Miranda, Sonia; 1032
Moranne, Olivier; 142, 742
Morawski, Bozena; 838, 838
Moreau, Kerrie; 859, 859
Moreno, Santiago; 266, 579, 918
Morgan, Ethan; 1006, 1070
Morgan, Timothy; 151LB
Morgand, Marion; **345**
Morgello, Susan; 492, 498
Mori, Masahiko; **275**, **276**, **921**
Morin, Mylène; 351
Morlat, Philippe; 142, 742
Morón-López, Sara; 414, 432
Morrell, Craig N.; 476
Morris, Alison; **490**
Morris, Danielle D.; 1103
Morris, Lynn; 908
Morris, Sheldon; 300, 304, 300, 304, 330
Morris, Sheldon R.; 1020
Morrison, Charles S.; 622, 622
Morse, Caryn; 485
Morse, Gene D.; 517, 542
Mortier, Emmanuel; 373
Morton, Jennifer; 969
Morwabe, Alex; 625, 624, 625
Mosbah, Amor; 213
Moscoe, Ellen; 1110, 1110
Mosepele, Mosepele; **734**
Moser, Carlee; 140
Moser, Kathleen S.; 828LB
Moses, Agnes; 719
Moses, Samual; 618
Moshiro, Candida; 1076
Moss, Darren M.; **519**
Motloung, Ming-Han; 581
Moulton, Larry; 374
Mounzer, Karam; 376, 975
Mourez, Thomas; 232
Mousseau, Guillaume; 413
Moy, Carolyn; 658, 668
Moya, Andrés; 266
Moyo, Faith; 781, 781
Moyo, Sikhulile; 247, **630**, 871, 990
Møller, Holger Jon; 316
Mpendo, Juliet; 1038
Mpoudi-Ngole, Eitel; 231
Msweli, Sthembiso; 256, 256
Mtande, Tiwonge; 874
Mthiyane, Hloniphile; 603
Mthiyane, Thuli; 92
Mu, Weiwei; 56
mudd, joseph C.; 298LB
Muddiman, David C.; 535, 535
Mudrikova, Tania; 243
Muenchhoff, Maximilian; 921
Mufamadi, Grace; 830
Muganzi, Davis C.; **976**
Mugavero, Michael J.; 578, 1004, 1005
Mugo, Nelly; 24, 290, 980, 981, 983
Mugusi, Ferdinand; 606, 809
Mugwaneza, Placidie; 865, 865
Mugwanya, Kenneth K.; **981**
Mugyenyi, Peter; 552, 595, 941
Muhammad, Mukhtar Y.; 558
Muir, Andrew; 688
Mujugira, Andrew; 988, **989**
Mujuwisha, Louis; 700
Mukarugwiro, Beata; 1087, 1087
Mukherjee, Pranab K.; **844**
Mukim, Amey; 407
Mukisa, Gerald; 1067
Muktiarti, Dina; 915
Mukui, Irene; 32, 153, 625, 624, 625, 1079
Mulawa, Dominic; 885
Mulenga, Lloyd; 808
Mullen, Michael; 90
Müllhaupt, Beat; 150
Mullins, James; 55LB, 107
Mullis, Caroline E.; 673
Multicenter AIDS Cohort Study, Neuropyschology Working Group O.; 493
Munamunungu, Virginia; 808
Munch, Jan; 208
Munderi, Paula; 94
Münk, Carsten; 849
Munro, Cynthia A.; 463, 493, 494
Murakami-Ogasawara, Akio; 264, 265
Murillo, Wendy; 607
Murnane, Pamela; 290
Murphy, Gary; 626, **618**, 626, 1042
Murphy, James R.; 922
Murphy, Kerry; 858, 858
Murphy, Robert L.; 140
Murray, Lyle W.; **818**
Murrell, Ben; **259**, 491, 496
Murry, Jeff; 417
Murugavel, Kailapuri G; 704
Muscatello, Antonio; 466
Mushiroda, Taisei; 295
Musiime, Victor; 927, 951
Musinguzi, Nicholas; 556, 976
Musoro, Godfrey; 457
Mussana, Helen; 457
Musselwhite, Laura W.; **308**
Mussini, Cristina; 562
Musubire, Abdu; 836, 838, 836, 838
Musumeci, Giuseppina; 773
Mutabaruka, Alphonse; 1087, 1087
Mutabazi, Vincent; 700
Mutevedzi, Tinofa; 896, 1102
Mutimura, Eugene; **780**, **780**
Muyinda, Abdu-Maliki; 1039
Muzaale, Abimereki D.; 783
Muzoora, Conrad; 722
Mvula, Natasha Z.; 1078
Mwamzuka, Mussa; 278
Mwanahamuntu, Mulindi; 710
Mwangwa, Florence; 740
Mwebaza, Norah; 513
Mweemba, Aggrey; 457
Mwelase, Thando; 778, 778
Mwimanzi, Francis; 228
Mwimanzi, Philip; **536**
Myburgh, Renier; 104LB
Myer, Landon; 26LB, 34, **864**, 857, **864**, 888
Myers, Julie; 1001
Myers, Robert A.; 613
Myers, Timothy; 311
Mylvaganam, Geetha H.; **370**
Mzembe, Themba; 816LB, 885
Mziray, Hawa; 1086, 1086

– N –

Nabeta, Henry W.; 836, 573, 826, 836
Naggie, Susanna; **152LB**, 750, 750
Naicker, Nivashnee; 984
Naidoo, Anushka; **984**
Naidu, Kevindra K.; 1110, 159, 1110
Nair, Govind; 485
Nair, Kavita; 652
Nakagawa, Fumiyo; 1117
Nakalema, Shadia; 85LB, 1067
Nakamoto, Beau K.; 754
Nakanjako, Damalie; **322**
Nakasujja, Noeline; 452, 453, 454, 458
Nakigozi, Gertrude; 452, 453, 454, 458
Nakiyingi-Miiro, Jessica; 161
NALINTYA, ELIZABETH K.; **573**
Nalivaika, Ellen; 42
Nalugoda, Fred; 28, 30, 1084, 1088, 158, 321, 1036, 1084, 1085, 1088
Nalutaaya, Annet; 1038
Namagembe, Rosemary; 459
Namakula, Rhoda; **817**
Namkung, Yuree; 627
Nankya, Immaculate; 215, 595
Napravnik, Sonia; 580
Naqvi, Alissa; **650**
Naranbhai, Vivek; 987

Narasipura, Srinivasa; 508
Nardo, David; 686
Narla, Venkata A.; **759**
Nash, Denis; 1001
Nason, Martha; 987
Nasrullah, Muazzam; **613**
Nassau, Tanner B.; 1028
Nath, Avindra; 468, 485, 505
Nattermann, Jacob; 678, 679, 680
Natureeba, Paul; 883, 887
Navar-Boggan, Ann Marie; 750, 750
Navarro, Jordi; 414, 714
Navarro, María Luisa; 942
Navarro, Marisa; 918
Navarro Gomez, Maria Luisa; 937, 950
Ndase, Patrick; 988
Ndatimana, Dieudonne; 865, 865
Ndawinz, Jacques D.; **1077**
Ndayisaba, Gilles F.; 865, 865
Ndhlovu, Lishomwa C.; 754, 796
Ndhlovu, Zaza M.; **359**
Ndiaye, Abdoulaye; 807
Ndirangu, Jacqueline; 852
Ndivo, Richard; 632LB
Ndlovu, Nontobeko; 823
Nduati, Ruth W.; 162
Nduati, Ruth; 884
Nduati, Ruth W.; 889, 906, 945
Ndukwe, Lillian; 800
Ndung'u, Thumbi; 339
Ndung'u, Thumbi; 198, 359, 921
Neaton, James D.; 761
Neau, Didier; 146
Neblett Fanfair, Robyn; 842
Nega, Melon T.; 286
Negredo, Eugenia; 331, **767**
Negron, Jordi J.; 53, 360
Neidleman, Jason; 209
Neifer, Stefan; 671
Nel, Annalene M.; **524**, **995**
Nelson, Amy; 689, 692, 694, 695
Nelson, George W.; 197
Nelson, Julie A.; 33, 886, **909**
Nelson, Mark; 670
Nere, Marie Laure; 429
Nerlander, Lina M.; 1031
Neth, Olaf; 934, 942
Neubauer, George H.; 430
Neuhaus, Jacqueline; 761
Nevot, Maria; **587**
Newell, Kevin; 321
Newman, Laura; **945**, 946
Newton, Alicia; 696
Nfanyana, Kebatshabile; 810
Ng, Hwee; 365
Ng, Oon Tek; 557
Ng, Roland C.; 796
Ng'wanakilala, Touma; 1086, 1086
Ngan, David; 802
Ngo-Giang-Huong, Nicole; 788, 831
Ngono, Laure; 233
Ngono, Valérie; 233
Ngoupo, Paul Alain T.; **233**
Ngure, Kenneth; 969
Nguyen, Damhnien; 481
Nguyen, Quy; 40, 288
Nguyen, Thi Huyen Tram; 148
Nguyen, Truong V.; 943
Nicastri, Emanuele; 611
Nicholas, Paton; 457
Nichols, Brooke E.; **1105**
Nichols, Sharon; **450**
Nichols, Sharon L.; **936**
Nickel, Gabrielle; 215
Nicol, Mark P.; **130**
Nicol, Mark; 823
Nielsen, Kirsten; 834, 834
Nielsen, Kristen; 838, 838
Nielsen, Patricia S.; 325
Nijhuis, Monique; **403**, 538, **549**
Nikolaitchik, Olga A.; 45
Nilmanat, Ampaipith; 831
Nilsson, Staffan; 59, 470
Niska, Richard; 635
Niyonzima, Nixon; 400
Njorge, Anne; 946
Njoroge, Anne; 945
Njoroge, Julia; 800, 1081
Njouom, Richard; 233
Njuguna, Irene N.; **911**
Njuguna, Pamela; 584
Nkambule, Rejoice; 1013
Nkengasong, John; **178**
Nkosi, Thandeka; 359
Noel, Nicolas; **333**
Noguera-Julian, Antoni; 923, 934
Noguera-Julian, Marc; 260, 261
Nohpal, Adriana; 117
Noorhasan, Marisela; 804
Norder, Helen; 664
Nordly, Sannie; 877
Normark, Johan; 700
Northbrook, Sanny Y.; 1032
Noto, Alessandra; 422
Nouvet, Franklin; 214
Novak, Richard; 997
Noviello, Stephanie; 151LB
Novitsky, Vladimir; **247**, 630
Nowicka-Sans, Beata; 539
Noy, Ariela; **70**
Nsanzimana, Sabin; 157, 1109
Nshom, Emmanuel; 880
Ntakakirabose, J.D.; 1087, 1087
Ntakpe, Jean Baptiste; 115LB
Nuñez, Esmeralda; 937
Nuñez-Rubio, Sandra; 607
Nunn, Andrew J.; 94
Nunnari, Giuseppe; 776
Nunoya, Junichi; 677
Nussenzweig, Michel; 346
Nuttall, Jeremy P.; 524
Nuwagaba-Biribonwoha, Harriet; 155, 938
Nwokolo, Nneka; 961, 961
Nyaguara, Amek; 161
Nyirenda, Moffat; 1046
Nyoni, Cynthia; 1091

– O –

O-charoen, Pichaya; 796
O'Brien, Daniel P.; 1011
O'Brien, Meagan; **284**, 323
O'Bryan, Thomas; 565
O'Connell, Robert; 841
O'Connor, David; 363
O'Connor, Jemma L.; 761
O'Doherty, Una; 384, 390, 384, 390
O'Halloran, Jane A.; **732**
O'Keefe, Barry; 968
O'Riordan, Mary Ann; 925
O'Sullivan, Eithne; 332
Oakes, Mariah; 541
Oberle, Corinna S.; **218**
Obermeier, Martin J.; 671
Obimbo, Elizabeth M.; 945
Ocfemia, M. Cheryl; 241
Odanga, Irene A.; 817
Odeh, Mouneer; 145
Odem-Davis, Katherine; 861, 861, 906
Odeny, Thomas; 584
Odevall, Lina; 382
Odhiambo, Collins; 625, 625
Odongo, Florence; 37, 927
Odoyo, Josephine; 969
Ofotokun, Igho; 860, 515, 860
Ogata, Yoko; 227
Oh, Eugene; 385
Oishi, Shinya; 589
Oka, Shinichi; 143LB, 328
Okafor, Ogechi; 533, 533
Okal, Duncan; 632LB
Okeke, Nwora L.; 750, 750
Okello, Velephi; 155, 938
Okonkwo, Prosper; 940, 1015, 1075
Oksendenhendler, Eric; 429
Okui, Lillian; 247, 630
Okulicz, Jason F.; 565
Okurut, Samuel; 834, 815, 834
Okvist, Mats; 352
Oladokun, Regina; 940
Olagunju, Adeniyi; **533**, **533**
Olaitan, Oluremi; 940
Olejemeh, Christie; 854
Olejniczak, Natalia; 86LB
Olesen, Rikke; **369**, 405
Oleske, James; 917
Oleske, James M.; 944
Olivares, Isabel; 347
Olive, Andrew; 357
Oliveira, Maureen; 591
Olivier, Kenneth; 812
Olivieri, Kevin; 40, 43
Olivieri, Kevin C.; **288**
Olmstead, Andrea; 697
Olson, Ashley; **602**, **1051**
Olson, Julia; 588
Olson, Lana M.; 515
Olson, Mary C.; 644, 644
Olszak-Olszewski, Michael; 1114, 1114
Omar, Ifrah; 189
Omar, Tanvier; 89, 825
Omenda, Maxwel; 906
Omondi, Harrison; 625, 625
Omondi, Harrison Fredrick; 624
Omondi, Milton; 764
Ondoa, Pascale; 574
Onen, Nur; 713
Onwuatuelo, Ifeyinwa; 1015
Onyekwena, Obinna; **1114**, **1114**
Op de Coul, Eline; 1007, 1117
Opollo, Valarie; 624
Orazulike, Ifeanyi K.; 1063, 1063
Orden, Samuel; 735
Orem, Jackson; **71**, 88
Orido, Millicent; 597
Orikiiriza, Judy T.; **700**
Orkin, Chloe M.; 332
Ormsby, Christopher; 848
Orofino, Giancarlo; 487
Orrell, Catherine; **559**, 1080
Ortega, José; 627
Ortega, Mario; 447, 488
Osei-Kuffour, Edmund; **849**
Osinusi, Anu; 148, 653, 689, 692, 694
Osiyemi, O; 893
Oster, Alexander; 166
Oster, Alexandra M.; 120, **241**
Oster, Alexandra; 1043
Østergaard, Lars; 109, 369, 405
Ostrowski, Mario; 271
Ostrowski, Matias; 320
Osuna, Christa E.; 108
Otero, Maria del Carmen; 942
Otieno, Fred; 632LB
Otieno, Vincent; 911
Otis, Joanne; 251
Otwombe, Kennedy; 35
Ouchi, Dan; 283, 331, 414
Ouyang, Zhengyu; 185
Overbaugh, Julie M.; 861, **126**, 162, 866, 223, 280, 861, 866, 884, 906, 945, 983, 1035
Overton, Edgar T.; **772**, 787
Owen, Andrew; 84, 532, 533, 519, 527, 532, 533
Owen, MIchele; 621
Owen, S. Michele; 620
Owens, Douglas K.; 1121

– P –

P, Nandagopal; 641
Pace, Craig S; 345
Pace, Matthew; 111LB
Paczuski, Pawel; 140
Padgett, Denis; 833
Paduta, Dzmitry; 561
Pagani, Nicole; 487
Paganini, Sara; 168
Pagano, Marcello; 612, 612
Pahwa, Savita; 310, 947
Paiardini, Mirko; 168, 298LB
Paillart, Jean-Christophe; 193
Pajkrt, Dasja; 935
Pal, Ranajit; 966LB
Palanee-Phillips, Thesla; 1033
Palazzo, Adam; 530
Palefsky, Joel; 713
Palella, Frank J.; 649, 747, 748, 649, 743, 747, 748, **749LB**, 786, 797, 997
Palk, Laurence; **1034**
Palladino, Claudia; **950**
Pallikkuth, Suresh; 947
Palma, Paolo; 947
Palmer, Chrstine D.; 307
Palmer, Clovis S.; **320**
Palmer, Sarah E.; **109**, 382
Palombi, Leonardo; 879
Palou, Elsa Y.; 242
Palou, Elsa; 601, 607
Paltiel, David; 1104, 1119, 1104, 1119
Palucka, Karolina; 353
Palumbo, Paul E; 36, 939

Panayidou, Klea; **913**, **1094**
Panayotova-Dimitrova, Diana; 395
Pancera, Marie; 345
Panchia, Ravindre; 26LB, 1033
Pandrea, Ivona; **268**, 406, 965
Pang, Phillip S.; 82, 148, 152LB
Panichsillapakit, Theppharit; **600**
Paniez, Hubert; 146
Panigrahi, Soumya; **298LB**
Panousis, Constantinos; 982
Pantaleo, Giuseppe; 422
Papasavvas, Emmanouil; **376**
Pape, Jean; 156
Pape, William J.; 546, 1012
Papp, Eszter; 902
Papp, John; 962, 963
Pappa, Keith; 550
Para, Michael; 110LB
Paraskevis, Dimitrios; **229**, 602
Paredes, Roger; 260, 261, 964
Parera, Mariona; 260, 261, 587
Parikh, Sunil; 513
Parikh, Urvi M.; **982**, 985
Park, Lawrence; 750, 750
Park, Sangeun; 365
Park, Sung Yong; 254, 254
Parker, Gary; 830
Parker, Kara; 588
Parker, Kate; 541
Parker, Monica M.; 664
Parker, Robert; 1119, 1119
Parkes-Ratanshi, Rosalind M.; 563, **1067**
Parkhill, Julian; 816LB
Parniak, Michael; 585
Parruti, Giustino; 699
Parry, John; 618
Partridge, Thomas; 169
Pascale, Juan M; 242, 601
Passeri, Laura; 443
Passmore, Jo-Ann; 314, 857
Pasternak, Alexander; **384**, 390, **383**, **384**, 390
Patassi, Akouda; 807
Pate, Kelly A.; **476**
Patel, Bharati; 618
Patel, Eshan U.; 1084, 98, 321, 623, 667, **673**, 1084
Patel, Faeezah; 930, 932
Patel, Kunjal; 931, 933
Patel, Kushang V.; 783
Patel, Neal M.; 149, 648, 648
Patel, Pragna; **713**, 772
Patel, Priya; 365
Patel, Vipulkumar; 61
Pathak, Vinay K.; 45
Pather, Arendevi; 1033
Pathipvanich, Panita; 275, 276
Patnaik, Padmaja; 1029
Paton, Nicholas; 57, **119**, 552, 595
Patrat, Catherine; 1122
Patrick, Ingiliz; 646, 646
Pattacini, Laura; 290
Pattanasin, Sarika; 635, 1026
Patterson, Thomas L.; 1024
Patterson-Lomba, Oscar; 612, 612
Patton, Lauren; 844
Pau, Alice K.; 520
Pau, Chou-Pong; 993
Paul, Biswajit; **401**
Paul, Robert H.; 447
Pauls, Eduardo; 204, 205
Paxinos, Ellen; 259
Payne, Brendan A.; **785**
Payne, Helen A.; **35**
Payne, Rebecca P.; 362
Paz-Bailey, Gabriela; **1060**, 850, 998, 1031, 1041, 1058, **1060**, 1115
Peavy, Hannah H.; 801
Pedersen, Court; 561
Pedersen, Gitte; 877
Peer, Cody; 87
Pegu, Amarendra; 50, 167
Pei, Luxin; **813**
Peloquin, Charles A.; 828LB
Peluso, Michael; 473
Pence, Brian W.; 851
Pencina, Michael; 750, 750
Penlap Mbeng, Véronique; 233
Penman, Celia; 662
Penrose, Kerri J.; **985**
Penugonda, Sudhir; 649, 463, 649
Penzak, Scott R.; 520
Perbost, Isabelle; 650
Pereira, Lara E.; 510
Perelson, Alan S.; 690
Perelson, Alan S; 254, 148, 254
Pereyra, Florencia; 185, 227
Perez, Idene E.; 666
Pérez, Jorge; 338
Pérez, Lissette; 338
Pérez-Álvarez, Nuria; 767
Perez-Bercoff, Danielle; 633
Perez-Bernal, Mercedes; 414
Perez-Diez, Ainhoa; 311
Perez-Elias, M Jesús; 553
Pérez-Latorre, Leire; 657
Pérez-Santiago, Josue; 375
Pérez-Santiago, Josué; 263, 331, 456, 491, **496**, 499
Perilhou, Anais; 867
Perlman, David; 647
Permar, Sallie R.; **174**
Permar, Sallie; 903, 904, 905
Pernas, Maria; **347**
Perno, Carlo Federico; 699
Perno, Carlo-Federico; 611, 702
Perreau, Matthieu; **422**
Perro, Mario; 357
Perry, Michelle R.; 238
Persaud, Deborah; 33, 374, 396
Perseghin, Paolo; 466
Persing, David; 91
Perti, Tara; 27
Perumalswami, Ponni V.; 149, **648**, **648**
Pesano, Rick L.; 145
Peterman, Thomas A.; 855
Peters, Lars; 637
Peters, Marion G.; **17**, **182**, **639**, 676
Peters, Philip J.; 620, 1003, 1018, 1069
Peters, Philip; 1082
Peters, Zachary J.; 1103
Petersen, Janne; 316
Petersen, Maya; 1056
Petersen, Maya L.; 1071
Petersen, Maya; 1101
Petersen, Tess L.; 692
Peterson, Christopher W.; **433**
Peterson, Julia; 60, 62, 475
Petlo, Chipo; 870
Petrechko, Oksana; 214
Petro, Greg; 888
Petropoulos, Christos J; 121, 696
Petrovas, Constantinos; 49, **167**
Petz, Lawrenze D.; 432
Peyper, Janique; 811
Peytavin, Gilles; 564, **891**
Pfafferott, Katja J.; 169
Pfeifer, Nico; 338, 343
Phanuphak, Nittaya; 272, 473, 841, 943, 1019LB
Phanuphak, Praphan; 779, 557, 779, 841
Philip, Neena M.; 1013
Phillips, Andrew N.; 315, 560, 582, 761, 805, 1117
Phillips, Rodney; 111LB, 818
Phillips, Tamsin; 864, 864, **888**
Pho, Mai T.; 844
Phofa, Rebecca; 895
Phuang-Ngern, Yuwadee; 272
Phung, Pham; 259
Pialoux, Gilles; 23LB
Pianowski, Luiz; 416
Piatak, Mike; 168, 420, 948
Pickering, Aaron; 651, 651
Pickles, Mike; 249, 1048
Picton, Anabela; 314
Pierce, Anna; 958, 958
Pierre, Samuel; **156**
Pietz, Harlan L.; 400
Piggott, Damani A.; **783**
Pike, Emily; 1018
Pilcher, Christopher D.; 626, 208, **209**, 386, 626
Pillai, Satish; 386
Pillay, Deenan; 256, 1110, 159, 248, 256, 596, 603, 896, 991LB, 1102, 1110
Pillay, Sureshnee; 256, 256, 603
Pillay, Yogan; 154
Pineda, Juan A.; 709
Pineda-Peña, Andrea-Clemencia; 338
Pineda-Tenor, Daniel; 682
Pinedo, Yvette; 545
Ping, LiHua; 221
Pingen, Marieke; 243
Pinillos, Francoise; 930, 932
Pinnetti, Carmela; **63**, 562, 636
Pino, Maria; **283**
Pinto Cardoso, Sandra M.; 264, **265**
Pinyakorn, Suteera; 47
Pinyakorn, Suteeraporn; 841
Pinzone, Marilia R.; **776**
Piroth, Lionel; **146**, 701
Pisaturo, Mariantonietta; 702
Pissani, Franco; 166
Pitsiu, Maria; 509
Pitt, Blanche; 1103
Pitts, Robert A.; **715**
Piwowar-Manning, Estelle; 629
Plana, Montserrat; 391, 354, 391, 960
Planelles, Vicente; 424
Plankey, Michael; 489, 639, 743
Plantier, Jean-Christophe; 257, 230, 232, 233, 257, 345
Plazzi, Maria Maddalena; 63
Plenty, Albert; 883
Plesa, Gabriela; 402
Plishka, Ronald; 503
Plotkin, Marya; 1086, 1086
Plückthun, Andreas; 351
Plummer, Francis; 287
Podack, Eckhard R.; 273
Podany, Anthony T.; 84, 511
Podzamczer, Daniel; 113LB
Pohlmeyer, Christopher W.; **427**, **427**
Poignard, Pascal; 259, 345
Poizot-Martin, Isabelle; **575**
Polacino, Patricia; 348, 433
Polgreen, Philip M.; 1083
Policicchio, Benjamin; 268, **406**, 965
Polis, Michael; 689
Polis, Michael A.; 692
Polis, Michael; 694
Polizzotto, Mark N.; **87**, 399
Pollack, Ross; 392, 392
Pollard, Richard; 267, 548
Polo, Miriam; 500
Polonis, Victoria R.; 170LB
Poluektova, Larisa; 504, 528, 543
Polyak, Christina S.; 459
Polyak, Christina; 764
Poon, Art F.; 592, 598
Poordad, Fred; 687, 688
Popov, Mikhail; 494
Porcella, Stephen; 869
Porras-Cortes, Guillermo; 242, 601
Portegies, Peter; 472
Porter, Danielle P.; **605**, **952**
Porter, Kholoud; 602, 1042, 1051
Post, Frank A.; 143LB, 768, 794, 795, 798
Post, Jeffrey J.; **628**
Post, Wendy; 743
Posthouwer, Dirk; 669
Potempa, Marc; **42**
Poulsen, Susanne D.; **325**, 758, 803
Poulson, Hahhah; 919
Poveda, Jean-Dominique; 232
Power, Chris; 448, 465, 467
Power, Christopher; 471
Powers, Kimberly A.; 851, 1044
Powis, Kathleen M.; **870**, **876**
Pozniak, Anton; 113LB, 795, 1118
Prachanronarong, Kristina; 693
Prasad, Paras N.; 542
Prasad, Ramakrishna; **651**, **651**
Prasitsuebsai, Wasana; 943, 951, 953, 956
Pratt, Lindsay; 652
Praygod, George; 762
Preiser, Wolfgang; 616
Prejean, Joseph; 1060, 1060
Prendergast, Andrew; **941**
Prendergast, Andy; 921
Pressiat, Claire; **512**
Prestage, Garrett; 1019LB
Pretorius, Karyn; 359
Price, Alison; 583, **1046**
Price, Angie; 653, 695
Price, Lance; 1085
Price, Matthew; 1044
Price, Richard; 59, 60, 62, 439
Price, Richard W.; 440
Price, Richard; 445, 474, 475, 760
Price, Sarah; 416

Prieto, Luis; 937
Primmer, Irene; 49
Prins, Jan; 383
Prins, Maria; 602, 674, 806, 1051
Procopio, Francesco; 422
Prodger, Jessica; 1085
Promny, Dominik; 730
Proschan, Michael; 581
Prosperi, Mattia; 655
Protack, Tricia; 539
Prozesky, Hans; 724, 724
Puertas, Mari Carmen; 414
Puertas, Maria C.; 432
Puga, Ana; 450
Pugliese, Pascal; 650
Puig, Jordi; 767
Pula, Selloane; 581
Puligujja, Pavan; **528**
Puoti, Massimo; 636
Purcell, Damian F.; 412
Purcell, Tony; 412
Purdy, Julia B.; 683
Purdy, Julia; **756**
Purdy, Julia B.; **928**
Puren, Adrian J.; 154
Purswani, Murli; **933**
Purswani, Murli U.; 944
Pusoentsi, Malebogo; 711
Putcharoen, Opass; 703
Puttamaswin, Suwanna; 47
Puttkammer, Nancy; 875
Pyakurel, Ashmit; 60
Pym, Alexander; 830
Pyndiah, Nitisha; **191**, **191**

– Q –

Qi, Huilin; 371
Qin, Min; 31LB, 924
Quashie, Peter K.; 591
Quayle, Alison; 211
Queen, Suzanne E.; 416, 476
Quenneville, Simon; **11**
Querol, Sergi; 432
Quinn, Jeffrey; 380, 673
Quinn, Thomas C.; 28, 30, 1084, 98, 321, 623, 667, 673, 869, 1084, 622, 622, 987
Quinten, Chantal; 1117
Quirino, Tiziana; 765
Quirk, Erin; 952, 953, **954**
Quiroga, Maria F.; 821

– R –

Rabie, Helena; 920
Raboud, Janet; 777
Rachlis, Anita; 448, 465, 467, 1053
Rachlis, Beth; **1072**
Radovic-Moreno, Aleksandar F.; 357
Radzio, Jessica; **962**
Raehtz, Kevin; 965
Raengsakulrach, Boonyos; 986
Rafecas, Antoni; 640
Raffe, Sonia; 961, 961
Raffi, François; 727, 727, 766
Ragin, Ann; 494
Ragni, Margaret; 799
Ragonnet-Cronin, Manon L.; 249, **253**
Ragupathy, Viswanath; **258**, **258**
Rahimy, Elham; **62**
Rahkola, Jeremy; 834, 834
Raifman, Julia; **896**
Rainford, Louise; 732
Rainho, Jennifer N.; **361**
Rainwater, Stephanie; 1035
Rainwater-Lovett, Kaitlin; 374, **396**
Rajagopal, Sharanya; 27
Rajoli, Rajith; 531, 532, 531, 532
Rajulu, Deepa; 599
Rakhmanina, Natella; 953
Ralfkiær, Elisabeth; 325
Ramadhani, Angela; 570, 1076
Raman, Fabio; 756
Ramanathan, Srinivasan; 951
Ramarathinam, Sri; 412
Ramaswamy, Chitra; 729
Ramers, Christian B.; **661**
Ramgopal, M; **893**
Ramgopal, Moti; 795
Ramirez, Kristel P.; 589
Ramirez, Nora; 188, 188
Ramirez, Nora P.; 222
Ramji, Alnoor; 688
Ramjith, Jo; 864, 864
Ramlakhan, Yathisha; 339
Ramos, Eric M.; **627**
Ramos Amador, José Tomás; 937
Rampon, Osvalda; 923
Ramteke, Sarah; **930**, 932
Rannard, Steven P.; 527
Rantleru, Tumelo; 810
Rao, Srinivas; 50
Rapala, Alicja; 37
Rapista, Aprille; 211
Rasheed, Amna; 288
Rasmussen, Thomas A.; 109, 369, 405
Ratcliff, Annette; 215
Rath, Peter-Michael; 568
Rathore, Mobeen; 954
Ratmann, Oliver; 249, 252
Rattanamanee, Somprartthana; 438
Rauch, Andri; 150, 675
Raugi, Dana; 541
Raugi, Dana N.; **588**, 614
Rausch, Jason; 593, 593
Rausch, Michael; 670
Ravimohan, Shruthi; **810**
Ravindran, Palanikumar; 114LB
Rawizza, Holly E.; **940**
Rawlings, David J.; 401
Ray, Adrian S.; 82, 530
Ray, Michelle; 518
Ray, Neelanjana; 114LB
Ray, Stuart C.; 685
Raymond, Alice; 1118
Raymond, Henry F.; 1060, 1023, 1060
Razeghi, Sanam; **707**
Read, Tim R.; 958, 958
Reardon, Brian; **407**, 408
Rebeiro, Peter F.; **996**
Redd, Andrew D.; 28, 30, 321, **869**, 987
Reed, Jason B.; **175**
Rees, Helen; **26LB**
Reeves, Iain; 332
Reeves, Jacqueline; 696
Regan, Susan; 751, 734, 751, 1015
Regoes, Roland; 39
Regueiro-Ren, Alicia; 539
Reh, Lucia; **165**
Rehman, Andrea; 762
Reiberger, Thomas; 670
Reich, Daniel S.; 485
Reid, Matthew; 1014
Reid, Michael J.; 846
Reimann, Keith; 903
Reinberg, Thomas; 351
Reiss, Peter; 142, 252, 472, 579, 582, 659, 739, 742, 806, 935, 1007, 1048
Reitsma, Marissa; 597
Rekosh, David; 201
Remera, Eric; 157
Remien, Robert H.; 888, 1103
Ren, Weijia; 450
Reniers, Georges; **161**
Rentsch, Christopher T.; 746, 746
Requena, Mary; 274
Rerknimitr, Rungsun; 48, 272
Rerks-Ngarm, Supachai; 51, 170LB
Resino, Salvador; 682
Reszka-Blanco, Natalia J.; **225**
Rey, David; 146, 575, **701**, 1009
Reyes, Letty; 661
Reyes-Teran, Gustavo; 167
Reyes-Terán, Gustavo; 49, 242, 264, 265, 601, 607, 848
Reynes, Jacques; 727, 727, 793
Reynolds, Jessica L.; 542
Reynolds, Sandra; 463, 493, 494
Reynolds, Steven J.; 1088, **321**, 563, 1088
Rhein, Joshua; **836**, **838**, 826, **836**, **838**
Rhem, Catherine A.; 420
Ribaudo, Heather; 140
Ribaudo, Heather J.; 515
Ribaudo, Heather; 769LB, 787
Ribera, Esteve; 714
Rice, Charles M.; **18**
Rich, Asheligh; 1023, 1024, 1025
Richards, Elizabeth; **311**
Richards, Kristy; 719
Richards, Maureen H.; **508**
Richardson, Barbra A.; 162
Richardson, Barbra; 866, 853, 866, 884
Richardson, Barbra A.; 906
Richardson, Robyn; 958, 958
Richardson-Harman, Nicola; 966LB, 994
Richert, Laura; 353, 766
Richert-Spuhler, Laura E.; 286
Richman, Douglas D.; 219, 259, 263, 330, 375, 376, 386, 407, 409, 600
Richter, Clemens; 659, 669
Richter, Linda; 629
Richter-Haret, George; 406, 965
Ricottini, Martina; 63
Riddell, Lynn; 362
Riddler, Sharon; 1033
Rigdon, Joseph; 886
Rigodon, Jonas; 721
Rijnders, Bart J.; 566, 669, 674
Rimland, David; 728, 141, 746, 656, 728, 746, 1049
Rimola, Antonio; 640
Rinaldo, Charles R.; 389LB, 797
Rincón, Diego; 657
Rinke de Wit, Tobias F.; 118, 557
Rinke de WIt, Tobias F.; 574
Rios, Daniel; 370
Rios-Navarro, Cesar; 735
Ripamonti, Diego; 551
Ritter, Jana; 862
Rivadeneira, Emilia; 615
Riveira-Muñoz, Eva; 204, 205
Rivero, Antonio; 709
Rivero-Juarez, Antonio; **709**
Riyaten, Prakit; **788**
Rizzardini, Giuliano; 699
Roach, Margaret; 310
Roan, Nadia R.; **208**, 209
Robb, Merlin L.; 50, 51, 1063, 166, 272, 1063
Robbins, Danielle E.; **1045**
Robbins, Gregory; 136
Robbins, Rebekkah; 1069
Roberts, Allen; 584, **617**
Roberts, Owain; 532, 532
Roberts, Sarah T.; **980**
Robertson, Charles; 262
Robertson, Corne; 455
Robertson, David; 230
Robertson, Kevin; 60, 84
Robertson, Kevin R.; **439**
Robertson, Kevin; 440
Robertson, Kevin R.; 445, **451**
Robertson, Kevin; 452, 453, 454, 458
Robertson, Kevin R.; 475
Robertson, McKaylee; 1001
Robertson, Peter; 628
Robinson, Janet; 738
Robinson, John; 351
Roby, Gregg; 302, 302, 812
Rocafort, Muntsa; 260, **261**
Rockstroh, Juergen; 637
Rockstroh, Jürgen; 561, 670
Rockstroh, Jürgen K.; 678
Rockstroh, Jürgen; 679, 680
Rodger, Alison; 560
Rodriguez, Allan; 101
Rodriguez, Benigno; 684, 763
Rodriguez, Christophe; 564
Rodriguez, Gilhen; 922
Rodriguez Caprio, Gabriela; 90
Rodriguez de Miguel, Cristina; 960
Rodriguez-Barradas, Maria; 728, 141, 746, 728, 746, 1049
Rodriguez-Hart, Cristina M.; **1063**, **1063**
Rodriguez-Mora, Sara; **196**
Roederer, Mario; **10**, 55LB, 349
Rogal, Shari; 643
Roger, Michel; 251
Roger, Pierre Marie; 650
Rogers, Sam; 102
Rohan, Lisa; 993, 994
Rohr, Julia K.; **571**, 1091, **1120**
Rojanawiwat, Archawin; 275, 276
Rojo, Pablo; 942
Rojo Conejo, Pablo; 937
Rokx, Casper; **566**, 1105
Roland, Michelle E.; **799**
Rolland, Morgane; **51**, **55LB**, 170LB
Romano, Guillermo; 401
Romas, Laura; 269, **287**
Romas, Laura M.; 289
Romero, Laura; 273
Romero-Tejeda, Marisol; 307

Ronald, Allan; 292, 976, 981, 988
Ronan, Agnes; 888
Roosa, Heidi; 455, 482
Rosario, Debralee; 462
Rose, Charles; 101
Rose, Charles E.; 1060
Rose, Charles; 632LB, 635
Rose, Charles E.; 1060
Rose, Chuck E.; 1041
Rosebush, Julia C.; 925
Rosen, Elias P.; **535**, **535**
Rosen, Sydney; 781, 781, **1091**
Rosenberg, Eli S.; 973, **1115**
Rosenberg, Eric S.; 53
Rosenberg, Nora; 874
Rosenbloom, Daniel I.; 419
Rosenfeldt, Vibeke; 877
Rosenthal, Eric; 650
Ross, Douglas; 93
Ross, Lisa; 522
Ross, Michael; 142, 742
Rossetti, Barbara; 495
Rossi, Paolo; 947
Rossjohn, Jamie; 358
Roth, Eric; 1023, 1024, 1025
Roth, Norman; 733
Roth, Volker; 255, 255
Rothenberg, Jennifer; 140
Rothman, Richard; 98, 667
Rourke, Sean B.; **448**, **465**, **467**
Rousseau, Rodney; 271
Roussillon, Caroline; 139
Rouster, Susan D.; 690, 698
Rouster, Susan; 707
Routy, Jean-Pierre; 534, 251, 337, 534
Roux, Surita; 978LB
Rouzier, Vanessa; 156
Rouzioux, Christine; 52, 334, 373, 867
Rovira, Cristina; 960
Rower, Joseph; **81**
Rowneki, Mazhgan; 91
Roxby, Alison C.; **861**, **861**
Rua, Réjane; 237
Ruan, Chunhai; 43
Ruane, Peter; 151LB
Ruane, Peter J.; 691
Rubio, Rafael; 918
Rudakemwa, Emmanuel; 780, 780
Rudrik, James T.; 613
Rudy, Bret; 450
Ruel, Theodore; **883**
Ruelas, Debbie S.; **385**
Ruffin, Nicolas; 206, 353
Rugwizangoga, Eugene; **1087**, **1087**
Ruiz, Pedro; 43
Ruíz, Alba; 204, 205
Ruiz-Cruz, Matilde; **848**
Ruiz-Mateos, Ezequiel; 49
Rupert, Adam; 47, 302, 302, 308, 752, 928
Rusconi, Stefano; 562, 773
Rusert, Peter; 39, 165, 218, 351
Russell, Alex; 62
Russell, Anthony; 711
Russell, Marisa; 524
Rutstein, Richard; 1065
Ruxrungtham, Kiat; 703
Ryan, Emily; 168
Ryan, Jamie; 91
Ryan, Jeremy A.; 411
Ryan, R; 893
Ryom, Lene; 142, 582, 739, **742**, 805

– S –

Saafir-Callaway, Brittani D.; **854**
Saag, Michael S.; 837, 143LB, 152LB, 837
Sabatier, Jennifer; 615
Saberi, Sara; **901**
Sabharwal, Charulata J.; **1097**
Sabin, Caroline; 739, 742, 774, 805, 1051
Sabino, Ester C.; 1010
Sacktor, Ned; 451, **452**, 453, 454, 455, 458, 463, **482**, 489, 493, 494
Sadeuh-Mba, Serge Alain; 233
Sadler, Brian M.; 509
Saduvala, Neeraja; 120, 241
Saeidi, Alireza; 820
Sáez-Cirión, Asier; 52, 333
Saez-Llorens, Xavier; 954
Sagar, Manish; **217**
Sagay, Solomon; 1075
Sagnelli, Caterina; 702
Sagnelli, Evangelista; 702
Sahasrabuddhe, Vikrant; 710
Sahi, Sharon; 479, 840
Saidi, Yacine; 919
Saïdi, Hela; **285**
Sailasuta, Naponpon; 438
Sainz, Talía; 266, 267, **270**, 547, **918**, **942**
Sajadi, Mohammad; 1049
Sajja, Balasrinivasa R.; 504
Sakai, Keiko; **328**
Sakoda, Marissa; **484**
Sakr, Samah; 1081
Sakr, Sameh; 800
Salata, Robert A.; 844
Salazar-Austin, Nicole M.; **872**
Salazar-Vizcaya, Luisa P.; 150
Salazar-Vizcaya, Luisa; **675**
Saleem, Jawaad; 654
Salgado, Maria; 414, **432**
Salimo, Anna; 908
Salinas, Jorge L.; **746**, **746**
Salles, Nanci; 1010
Salomon, Horacio; 821
Salomon, Nadim H.; 647
Salumu, Leon; 1090
Salvadori, Nicolas; 788, **831**
Samandari, Taraz; 632LB
Samarawickrama, Amanda; **768**
Sambakunsi, Rodrick; 634
Sambatakou, Helen; 561
Samji, Hasina; **1055**
Samuels, David; 460
Sanchez, Ana; 258, 258
Sanchez, Rosa; 521
Sanchez, Travis; 973
Sánchez, Emilia; 934
Sánchez-Conde, Matilde; 657
Sanchez-Martinez, Javier; 705
Sanchez-Merino, Alberto; 347
Sanchez-Merino, Victor; 347
Sanchez-Ortega, Isabel; 432
Sanchez-Palomino, Sonsoles; 354
Sanchez-Silva, Aaron; 355
Sanders, Eduard J.; 102, **1044**
Sanders, Rogier; **164LB**
Sandkovsky, Uriel S.; **84**
Sando, David; 606
Sandstrom, Paul A.; 591
Sang, Norton; 740, 1056, 1101
Sangkum, Udomsak; 971, 986
Sanisetty, Srisowmya; 108
Sanne, Ian; 308, 313, 571, 829, 895, 1091, 1120
Santelli, John; **1036**
Santiago, Mario; 186
Santoro, Maria Mercedes; 611
Sapsirisavat, Vorapot; 703
Saracino, Annalisa; 655
Sarafianos, Stefan; 585
Saravanan, Shanmugam; **704**
Sardo, Luca; **45**
Sarfo, Fred S.; 849
Sarkar, Monika; 639
Sartori, Ana; 318
Satcher Johnson, Anna; 1040
Sather, Blythe D.; 401
Sattha, Beheroze; 306, 901
Satti, Iman; 818
Saunders, Terry; 289
Sauter, Daniel; **122**
Savant Landry, Ishani; **509**, **523**
Savitz, Alan; 449
Sawadogo, Adrien; 782, 576, 782
Sawanpanyalert, Pathom; 275, 276
Sawry, Shobna; 724, 724, 920
Sawyer, Sara; 223
Sax, Paul E.; **143LB**
Saylor, Deanna R.; 452
Saylor, Deanna; 453
Saylor, Deanna R.; **458**
Scagnolari, Carolina; **296**
Scangarello, Nancy; 645, 645
Scarsi, Kimberly K.; **85LB**, 940
Scarvaglieri, Elisabetta; 791
Scarvaglieri, Marielisabetta; 487
Schackman, Bruce R.; **1104**, **1104**, **1113**
Schadendorf, Dirk; 568
Schaefer, Jonas V.; 351
Schanz, Merle; 165
Scharen-Guivel, Valeska; 738
Schechter, Melissa; **302**, **302**
Scheffler, Konrad; 58, 239, 246, 435, 1020
Schenkel, Corinne; 218
Schenkwein, Diana; **381**
Scherpbier, Henriette J.; 935
Scherrer, Didier; 104LB
Scherzer, Rebecca; 731, 755, 757, 770, 784, 792
Schewe, Knud; 646, 646
Schiano, Thomas; 149, 648, 648
Schiffer, Celia A.; 42, 586, 693
Schinkel, Janke; 674
Schito, Marco; 258, 258
Schlaepfer, Erika; 207
Schlech, Walter; 1067
Schlucter, Mark; 744
Schmand, Ben A.; 472
Schmand, Ben; 935
Schmidt, Axel J.; 1008
Schmidt, Manfred; 381
Schmidt, Reinhold E.; 297
Schmutz, Guenther; 646, 646
Schmutz, Stefan; 255, 255
Schneider, Hannah; 476
Schneider, John A.; **1006**, **1070**
Schneider, Monika; 43
Schneider, Simon; 730
Schnippel, Kathryn; 829
Scholten, Stefan H.; 670
Schouten, Jeff; 451
Schouten, Judith; 472, 806
Schrack, Jennifer; 786
Schrier, Rachel D.; 330
Schroeder, Harry; 355
Schuetz, Alexandra; **272**, 480
Schuetze, Marcel; 671
Schultz, Bruce; 166
Schulze zur Wiesch, Julian; 206, 341
Schumm, Phil; 1006
Schüpbach, Jörg; 245
Schure, Allison L.; 411
Schürmann, Dirk; 114LB
Schutten, Martin; 566
Schutz, Charlotte; 835, 835
Schuurman, Rob; 243
Schwartz, Jill L.; 26LB
Schwartz, Olivier; 206
Schwartz, Sheree R.; **895**
Schwarzinger, Michaël; 1122
Sciaranghella, Gaia; 858, 858
Scott, Gwendolyn; 933
Scott, Hyman; **1017**
Scott, Rob; 731
Scott, Susan C.; 469
Scott-Algara, Daniel; **52**, 334
Scriven, James E.; **835**, **835**
Scully, Eileen; **307**
Seage, George; 917, 933
Seamon, Cassie; 692
Seamon, Catherine; 695
Seaton, Melanie; 478
Seaton, Melanie S.; 508
Sebastian, Thresia; **873**, 914
Secours, Rode; 546
Seddiki, Nabila; **206**, 353
Seifert, David; **255**, **255**
Seifert, Sharon M.; 83, **525**, 526
Sekaly, Rafick P.; **173**, 292, 388
Selke, Stacy; 27
Selvaggi, Carla; 296
Semba, Richard; 567
Seng, Rémonie; 373
Sereda, Paul; 1023, 1024, 1025
Sereti, Irini; 47, 48, 302, 268, 302, 308, 311, 337, 752, 772, 812, 813
Serghides, Lena; **902**
Serrano, Vanessa; 288
Serrano-Villar, Sergio; **266**, **267**, 270, **547**
Serwadda, David; 28, 30, 1084, 1088, 158, 321, 1036, 1039, 1084, 1085, 1088
Severe, Patrice; 156, 546
Sevinsky, Heather; 114LB
Sewankambo, Nelson K.; 1088, 1038, 1088
Seydi, Moussa; 541, 588, 614, 807
Shafiee, Hadi; 421LB
Shah, Maunank; **1108**
Shah, Monica; **144**
Shah, N. Sarita; **92**
Shah, Sharmila; 239, 1097
Shahabi, Kamnoosh; 271

Shahan, Judy; 98
Shahid, Aniqa; 536
Shaikh, Obaid; 643
Shaipanich, Tawimas; 802
Shalek, Alex; 185
Shan, Liang; **368**
Shankar, Anupama; 241
Shankar, Premlata; 356
Shao, Wei; 593, 105, 106, 109, 378, 399, 593
Shao, Yongwu; 953
Shapiro, David; 31LB, 894
Shapiro, Roger; 870, 871, 876, 878
Sharma, Amit; **223**, 280
Sharma, Anjali; **770**, **775**
Sharma, Monisha; 1111, 1111
Sharp, Victoria; 1065
Sharvadze, Lali; 664
Shattock, Robin; 86LB, 215
Shaw, Christiana M.; 44
Shaw, George M.; 44, 169, 349, 406
Shaw, Souradet Y.; **1054**
Shea, Thomas; 719
Sheaffer, Amy; 371
Shearer, Kate; 571, 1120
Shearer, William T.; **801**
Sheehan, Gerard J.; 732
Sheehan, Nancy; 534, 534
Sheikh, Virginia; 302, 302, 311, 812, 813
Shen, Gong; 82
Shen, Xiaoying; 904
Shepherd, Bryan E.; 517, 580, 741, 830, 833
Shepherd, Leah C.; 561
Sherman, David; 279
Sherman, Gayle; 910
Sherman, Kenneth E.; 151LB, **690**, 698, 707
Sherr, Lorraine; 560
Sheth, Anandi; 860, 860
Shi, Jing; 1000
Shi, Qiuhu; 780, 775, 780
Shiau, Stephanie; 141, 930, 932
Shiboski, Caroline H.; **716**
Shiboski, Caroline; 844
Shiels, Meredith S.; 717
Shih, Ivy H.; **1089**, **1089**
Shikuma, Cecilia M.; 480, 754, 796
Shikuma, Cecilia; 843
Shilaih, Mohaned; 199, 244, **245**, 253
Shimura, Kazuya; 589
Shindo, Keisuke; 200
Shinefeld, Jennifer; 1062, 1028, 1062
Shipper, Pauline J.; 538
Shiramizu, Bruce; 480
Shirazi, Talia; **468**
Shirk, Erin; 416
Shivakoti, Rupak; **567**
Shlipak, Michael G.; 792
Sholtis, Katherine; 372
Shopin, Dmitry; 1055
Shovlin, Margaret; 399
Siberry, George; 801
Sibisi, Zandile; 256, 256
Sibiya, Jacinta; 876
Sibley, Christopher; 756
Siccardi, Marco; 531, **532**, 519, 531, **532**
Sichali, Dorothy; 886
Sichali, Lifted; 816LB
Siddiqi, Azfar-e-Alam; **1052**
Sidharthan, Sreetha; **689**
Sidney, John; 364
Siedner, Mark; 556, 1059
Siefried, Krista J.; 441
Sieg, Scott; 298LB
Siegler, Aaron; 973
Sierra-Madero, Juan; 308
Sievert, William; 687
Siewe, Basile; 267, 270, 547
Sigaloff, Kim C.; 118
Sigaloff, Kim; 574
Sigel, Carlie; 715
Sigel, Keith; **728**, 715, **728**
Siliciano, Janet D.; 419
Siliciano, Robert F.; 392, 427, 368, 392, 397, 415, 419, 427
Silk, Rachel; 653, 694, 695
Silverberg, Michael J.; 726, 638, 726
Silverman, Rachel A.; **1081**
Silvestri, Guido; **2**, 168, 326
Simen, Arthur; 449
Simiele, Marco; 791
Siminski, Suzanne; 801
Simmons, Ann Marie; 91
Simmons, Bryony; 654
Simmons, Ruth; **1042**
Simoes, Marisol; 318
Simon, David; 799
Simon, Francois; 230, 345, 429
Simon, Karl Georg; 646, 646
Simon, Viviana A.; 187
Simonetti, Francesco R.; **105**
Simoni, Jane; 853
Simpson, Jessica L.; 1002
Sims, Stuart; 362
Sims, Zayani; 653, 689
Sin, Don; 802
Sinayobye, Jean D'Amour; 780, 780
Sinclair, Elizabeth; 270, 382
Singer, Elyse; 464
Singh, Kumud; **462**, 481, **924**
Singhania, Akul; 408
Singini, Isaac; 1047
Singletary, Tyana; 510
Singtoroj, Thida; 943
Sinha, Arjun; **755**
Sinigaglia, Elisabetta; 705
Sinsheimer, Janet; 464
Sinzahera, Jovite; 1087, 1087
Sionean, Catlainn; **1031**
Sirivongrangson, Pachara; 1026
Sirois, Patricia A.; 936
Sithinamsuwan, Pasiri; 480
Sivaraman, Vijay; 225
Siwale, Margaret; 118, 557
Siyunda, Alice; 808
Skaathun, Britt; 1006, 1070
Skanderson, Melissa; 141
Skarbinski, Jacek; 747, 747, 974, 1057, 1064, 1115
Skolasky, Richard; 482
Slaven, James E.; 737
Slaymaker, Emma; 161
Sleasman, John; 183, 450
Slike, Bonnie M.; 47
Slike, Bonnie; 48, 473
Slim, Jihad; 645, 645, 691
Sloan, Caroline E.; 975
Sloan, Derek D.; **417**
Sloan, Richard D.; 189
Sluis-Cremer, Nicolas; 423
Slyker, Jennifer A.; **884**, 911
Smit, Colette; **659**
Smit, Erasmus; 594, 596
Smith, Adrian D.; **102**
Smith, Bryan; 468
Smith, Bryan R.; **485**
Smith, Colette; 335, 560, 579, 582, 742
Smith, Davey M.; 239, 259, 330, 435, 456, 491, 499, 704, 1021, 1022
Smith, David M.; 300, 304, 391, 58, 219, 240, 246, 263, 300, 304, 375, 391, 492, 600, 1020
Smith, Elizabeth; 894
Smith, Graham H.; 554LB
Smith, James M.; 510
Smith, Jennifer; 89
Smith, Jennifer A.; **1111**
Smith, Jennifer; **1107**
Smith, Jennifer A.; **1111**
Smith, Jonathan; 92
Smith, Justin C.; 1041, 1058
Smith, Kimberly Y.; 550, 554LB
Smith, Kyle; 838, 838
Smith, Laura; 91
Smith, Lou C.; 599, 1002
Smith, Robert A.; **541**, 588, 614
Smith Fawzi, Mary C.; 809
Smith-Bradley, Candice; 521
Snow, Joseph; 468, 485
So-Armah, Kaku; **1049**
Sobieszczyk, Magdalena E.; 55LB
Sobolowski, Michele D.; 105
Sobolowski, Michele; 398
Sobotha, Christian; 114LB
Sodora, Don; **279**, 897
Sogni, Philippe; 701
Sohn, Annette H.; **943**
Solberg, Owen; 696
Soldati, Laura; 765
Soler-Palacín, Pere; 934, 950
Solomon, Ajantha; 109
Solomon, Sunil S.; 641, **1016**
Solomon, Sunil S; 704
Solomon, Suniti; 641, 704, 1016
Soltau, Marieke; 849
Some, Fatma; 1073
Sommerfelt, Maja A.; 352
Somsouk, Ma; 299LB
Song, Ivy H.; 522
Song, Ruiguang; 1052
Song, Xiao Yu; 1036
Sönnerborg, Anders; 602
Sonza, Con; 412
Soonthornvarcharin, Stephen; 43
Soontornniyomkij, Benchawanna; 481
Soontornniyomkij, Virawudh; 464, 499
Soria, Alessandro; 466
Soria, Jaime; 107
Sorond, Farzaneh A.; 760
Souda, Sajini; 871, 878
Soudeyns, Hugo; 881
Soulie, Cathia; **564**
Soumana, Djadé I.; **693**
Southern Africa, IeDEA; 920
Souza, Scott A.; 754
Sow, Papa Salif; 541, 588
Søgaard, Ole; 109
Søgaard, Ole S.; 369, 405
Spagnuolo, Vincenzo; 443, **773**
Speck, Roberto; 104LB, 207, 337
Spector, Stephen; 301, 301
Spector, Stephen A.; 387, 410
Spector, Stephen; 924, 933
Spelman, Tim; 281, 1011
Spencer, David; 781, 781
Spengler, Ulrich; 678, 679, 680
Sperling, Rhoda; 880
Spina, Celsa A.; 407, 409
Spindler, Jonathan; 106
Spinner, Christoph D.; 670, **730**
Spire, Bruno; 23LB
Spivak, Adam M.; 424
Spragg, Chelsea; **203**, **203**
Spreen, William R.; 554LB, 966LB
Springborg, Karoline; 325
Spudich, Serena; 60, 62, 438, **473**, 475
Squillace, Nicola; 466
Srevatsan, Srinand; 826
Srikrishnan, Aylur K.; 641, 1016
Srinivasa, Suman; **138**
Sripan, Patumrat; **863**, **863**
Sriporn, Anuwat; 1026
Ssali, John; 577
Ssamula, Kate; 577
Ssebbowa, Paschal; 321
Ssebuliba, Joshua; 513
Ssekandi, Ismail; 1038
Ssetaala, Ali; 1038
St. Clair, Marty H.; 554LB
Stablein, Don; 799
Stall, Ron; 743
Stamm, Luisa M.; 82, 152LB
Stankov, Metodi; **395**
Stary, Georg; **357**
Steenhoff, Andrew; 810, 846
Stefan, Cristina; 724, 724
Stein, James H.; 140
Steinbach, Sally; 468, 485
Steinberg, Seth; 87
Steininger, Katharina; 671
Steinmetzer, Katrin; 614
Stek, Alice; 892, 894
Stephan, Christoph; 381
Stephensen, Charles B.; 931
Stephenson, Kathryn E.; **430**
Sterjovski, Jasminka; 633
Sterling, Timothy; 741, 830, **833**, 900, 996
Sterne, Jonathan A.; 837, 576, 579, 837
Stevenson, Mario; 190, 361
Stewart, Annemie; 604
Sthreshley, Larry; 234
Stiegeler, Emanuel; **351**
Stinson, Kathryn; 920
Stirratt, Michael J.; 978LB
Stock, David A.; 545
Stock, Jenny; 268
Stock, Peter; 799
Stoll, Matthias; 297
Stolte, Ineke G.; 472, 806
Stone, Dan; 400
Stonier, Michele; 523

Storer, Norma; 137, 925
Storgaard, Merete; 877
Storim, Julian; 568
Stosor, Valentina; 649, 649
Strahm, Stefan; 103LB
Strain, Matt; 58, 375, 386, 435
Strain, Matthew; 376
Strassburg, Christian P.; 679, 680
Strbo, Natasa; **273**
Strebel, Klaus; 503
Streeck, Hendrik; **166**
Strehlau, Renate; 930, 932
Struchiner, Claudio; 1119, 1119
Study, HPV in Adolescents; 943
Sturdevant, Christa; 221
Stypinski, Daria; 522
Styrchak, Sheila; 107
Su, Amanda; 1104, 1104
Su, John R.; **839**
Su, Lishan; 225, 327, 677
Su, Tanja; 472
Suarez, Guadalupe V.; **821**
Suaysod, Rapeepan; 788
Suc, Bertrand; 274
Sudfeld, Christopher R.; **809**
Sudjaritruk, Tavitiya; 956
Sued, Omar; 821
Sugandhavesa, Patcharaphan; 778, 778
Suhr, Christina; 395
Sukrakanchana, Pra-ornsuda; 511
Sukwicha, Wichuda; 1026
Sulkowski, Mark; 147, 151LB, 152LB, **181**, 641
Sullivan, Meg; 101
Sullivan, Patrick; 973
Summers, Angela; 468
Suneja, Gita; 711, 718
Sung, Julia; 372
Sunpath, Henry; 1074
Suntharasamai, Pravan; 971, 986
Surenaud, Mathieu; 353, 819
Sussman Pena, Otto; 545
Sutha, Patama; 957, 957
Sutthichom, Duanghathai; 47
Svicher, Valentina; **702**
Swaims, Alison Y.; 860, 860
Swain, Carol-Ann; **1002**
Swamy, Manjunath; 356
Swanstrom, Ronald; 42, 112LB, 221, 439, 440, 445
Swarts, Avril; 89
Swartz, Talia; **323**
Sweet, Stephanie; 214
Swenson, Eugene S.; 687, **688**
Swenson, Luke C.; 117
Swindells, Susan; 84
Switzer, William M.; 120, 241
Swordy, Alice; 921
Sykes, Craig; 535, 535, 548
Symons, Jori; 549
Szabo, Eva; 777
Szadkowski, Leah; 777
Szpakowska, Martyna; 213
Szumilin, Elisabeth; 32, 153, 1079, 1090
Szwarcberg, Javier; 738

– T –

Tabano, David; 652
Taha, Taha; 869
Taiwo, Babafemi; **769LB**
Takamatsu, Yuki; 537
Takaori-Kondo, Akifumi; 200
Takeda, shunichi; 200
Takiguchi, Masafumi; 328
Takuva, Simbarashe; **154**
Taliani, Gloria; 636, 699
Taljaard, Marthinette; 1033
Tallada, Natalia; 714
Tamamura, Hirokazu; 590
Tamburrini, Enrica; 495
Tambussi, Giuseppe; 337
Tamuhla, Neo; 810
Tan, Darrell H.; **777**
Tanaka, Kazuki; 589
Tanaka, Yuetsu; 214
Tandon, Neeta; 149
Tang, Jun; 538
Tang, Lydia; 689, 694
Tang, Tian; 999, 1040
Tang, Weiming; **1096**
Tang, Winson; **434**
Tang, Yuyang; **214**
Tannenbaum, Pamela; 449
Tanner, Karen; 289
Tanriverdi, Kahraman; 759
Tanser, Frank; 1110, 159, 248, 603, 896, **991LB**, 1102, 1110
Tantale, Katjana; 104LB
Tantalo, Lauren; 479, 840
Tao, Xiaolu; 523
Tapia-Trejo, Daniela; 601, 607
Tastan, Cihan; 278
Tate, Janet; 746, 656, 746
Tattevin, Pierre; 727, 727
Taylor, Andrew; 963, 993
Taylor, Graham; 892
Tazi, Jamal; **104LB**
Tchendjou, Patrice; 233
Tchounga, Boris; 576
Teasdale, Chloe A.; 873, **914**
Tebas, Pablo; 310, 787, 975
Tebit, Denis; 201
Technau, Karl; 908
Technau, Karl-Günter; 724, 724, **910**, 920
Tedaldi, Ellen; 997
Teeraananchai, Sirinya; 956
Teferi, Gebeyehu; 683
Tegha, Gerald; 33, 868, 909
Teigler, Jeffrey E.; 166
Tejerina, Francisco; 682
Telenti, Amalio; 191, 191, 291
Teleshova, Natalia; 967, 968
Teller, Ryan; 992LB
Téllez, Norma; 264, 265
Tenorio, Allan; 763
Teodorof, Carmen; **481**
ter Stege, Jacqueline A.; 935
Tesselaar, Kiki; 549
Tettoni, Maria Cristina; 791
Thaingamsilp, Pramual; 831
Thanh, Nguyen T.; 843
Tharp, Gregory; 370
Theys, Kristof; **610**
Thiara, Diana; 756
Thiebaut, Rodolphe; **337**, 353, **569**, 576
Thielen, Alexander; 431, 605
Thientong, Varaporn; 957, 957
Thindwa, Deus; 634
Thio, Chloe; 638
Thirard, Laurence; 727, 727
Thirumurthy, Harsha; **1056**
Thomas, Aurielle M.; **653**
Thomas, David L.; 380, 641, 667
Thomas, Guajira; 649, 649
Thomas, Katherine; 290, 989
Thomas, Kevin; 455
Thompson, Corbin G.; 535, 535
Thompson, Corbin; **548**
Thompson, Jennifer; 57, 119, 457, 552, 595
Thompson, Melanie; 113LB, **545**
Thompson-Paul, Angela M.; **747**, **747**
Thomson, Kerry A.; **988**
Thongpaen, Suchart; 831
Thorne, Jennifer E.; 1053
Thornhill, John P.; 111LB
Thornton-Wells, Tricia A.; 461
Tian, Yuan; 539
Ticona, Eduardo; 107
Tidiane, Cheick Tidiane; 1077
Tiemessen, Caroline; 314
Tien, Phyllis; 639
Tien, Phyllis C.; 770, 775
Tierney, Ann; 308
Tierney, Camlin; 310
Tietjen, Ian; 536
Tiina, Ilmet; 278
Tilghman, Myres W.; 456
Tilton, John C.; 404
Tinago, Willard; **774**
Tincati, Camilla; 705, 773
Tindimwebwa, Edna; 969
Tine, Judicael; 807
Tipsuk, Somporn; 473
Tiraboschi, Juan Manuel; 86LB
Tise, Sarah; 81, 652
Tlali, Mpho; 825
Tobian, Aaron A.; 28, 30, 1084, 1084, 1085
Todd, Catherine S.; **857**
Todd, Jim; 570, 1076
Tolstrup, Martin; 109, 369, **405**
Toma, Jonathan; 696
Tomaras, Georgia D.; **65**
Tomaras, Georgia; 904, 905
Tomescu, Costin; **367**
Tommbe, Rachael; 1089, 1089
Tongo Passo, Marcel; **231**
Tongtoyai, Jaray; 1026
Töpfer, Armin; 255, 255
Torian, Lucia V.; 29, **99**, 239
Toro, Jessica; 553
Torre-Cisneros, Julian; 709
Torres, Berta; 959, 959
Torres-Torronteras, Javier; 204, 205
Torrone, Elizabeth A.; 839
Tosswill, Jennifer; 618
Tostevin, Anna; 596
Toth, Ilona; 341
Touloumi, Giota; 1051
Tovanabutra, Sodsai; 51, 55LB, 170LB
Townsend, Kerry S.; 689, **692**
Toyoda, Mako; **227**, 228
Tracy, Russell; 565, 1049
Traisathit, Patrinee; 788
Traite, Shirley; 944
Trautmann, Lydie; 413
Travers, Simon; 908
Treijtel, Nicoline; 524
Treluyer, Jean-Marc; 512, 949
Tréluyer, Jean-Marc; 863, 863
Tremblay, Cecile; 23LB
Trentini, Laura; 791
Trevillyan, Janine M.; **736**
Trevino, Samantha A.; 61
Triant, Virginia A.; **751**, 734, **751**
Trickey, Adam; 579
Trinh, Roger; 147, 691
Trinité, Benjamin; 426
Trkola, Alexandra; **39**, 165, 218, 351
Troia-Cancio, Paolo; 270, 547
Trombetta, John; 185
Trooskin, Stacey; 645, 645, **658**, **668**
Troseid, Marius; 758
Trottier, Benoit; 143LB
Trout, Rodney; 924
Truesdale, Aimee; 81, 518
Truong, Hong-Ha M.; **1010**
Truong, Khanh Huu; 956
Tsai, Alexander; 1059
Tsai, Angela; 417
Tsai, Hung-Chin; 235
Tsao, Li-Chung; **327**
Tsertsvadze, Tengiz; 664
Tsibris, Athe; **858**, **411**, 769LB, **858**
Tsiouris, Fatima; 873
Tsz-Shan, Kwong; 335
Tu, Xiongying; 356
Tubiana, Roland; 867
Tucker, Joseph; 1096
Tucker, Katie; **631**
Tumbare, Esther; 876
Tumikye, Adelline; 1067
Tumukunde, Dinah; 57
Tural, Cristina; 414
Turchin, Michael; 288
Turner, Megan; 741
Turner, Scott M.; 299LB
Turpin, Delmyra; 813
Turpin, Jim A.; 966LB
Turrziani, Ombretta; 296
Tursi, Nancy; 658, 668
Turville, Stuart G.; 1089, 1089
Tuyishime, Marina; **212**
Tye, Spencer; 449
Tzarnas, Stephanie; 658, 668

– U –

Ubolyam, Sasiwimol; 703
Udeagu, Chi-Chi N.; 1097
Ueno, Takamasa; 227, **228**
Uhr, Therese; 165
Uldrick, Thomas S.; 87, 399
Ulenga, Nzovu; 606
Ullum, Henrik; 325, 758
Unger, Elizabeth; 713
Unsal, Aylin; 928
Unutmaz, Derya; 278
Uprety, Priyanka; **374**, 396
Urassa, Mark; 161
Urban, Britta; 835, 835
Urban, Thomas J.; 518
Urday, Sebastian; 475
Uribe Leitz, Monika; 925

Urien, Saïk; 863, 863, 949
Uro-Coste, Emmanuelle; 814
Usadel, Susanne; 381
Usher, Christin; 447
Usmani, Shariq; 208
Utay, Netanya S.; **47**, 267, 270, 547

– V –

Vaag, Allan; 758, 803
Vai, Daniela; 487
Vaida, Florin; 56, 462, 488
Valade, Elodie; 949
Valantin, Marc-Antoine; 564
Valcour, Victor G.; **438**, **459**, 473, 480, 764
Valdes, Vanessa; 284
Valdivieso, Andres; 640
Valente, Susana T.; **413**
Valentin, Morgane; 891
Valere, Kimyata B.; **211**
Vallari, Ana S.; **234**
Vallejo, Alejandro; 266
Vallely, Andrew; 1089, 1089
Valls, Anna; 934
van Agtmael, Michiel; 1007
van Bel, Nikki; 540
Van Cutsem, Gilles; 32, **76**, 153, 555, 1014, 1079
van de Vijver, David A.; 566, 1105
van den Berk, Guido E.; 669
van der Heijden, Yuri F.; **830**
van der Horst, Charles M.; 33, 852, 868, 874, 886, 909
van der Meer, Jan T.; 669, 674
van der Sluis, Renee M.; **388**
van der Straten, Ariane; **979**
van der Valk, Marc; 659, 806
Van der Velden, Yme; 540
Van Dyke, Russell B.; 801
Van Dyke, Russell; 882
Van Dyke, Russell B.; 917, 931
Van Dyke, Russell; 933
van Gorp, Eric C.; 1105
van Griensven, Frits; 841
van Kasteren, Marjo; 892
Van Laarhoven, Arjan; 243
Van Laethem, Kristel; 338, 610
Van Lam, Nguyen; 915
van Lelyveld, Steven F.; 549
van Lunzen, Jan; 206, 341
Van Niekerk, Neliette; 524, 995
van Oosterhout, Joep; 57, 119, 552
Van Rie, Annelies; 895
van Rompaey, Stephen; 250
Van Rompay, Koen K.; 948
van Rooyen, Heidi; 1111, 1111
van Schalkwyk, Cari; 616
Van Schalkwyk, Julie; 901
van Sighem, Ard; 252, **1007**, 1048, **1117**
Van Wagoner, Nicholas; 1004
van Widenfeldt, Erik; 247, 630, 871
van Widenfelt, Erik; 876
van Zoest, Rosan A.; **472**
van Zoest, Rosan; 806
van Zyl, Gert U.; 604, 616, **912**
Vance, Patricia J.; 501
Vandamme, Anne-Mieke; 229, 338
Vandekerckhove, Linos; 377, 424, 549
Vanderford, Thomas H.; 286
Vandergrift, Nathan; 904
Vanhommerig, Joost W.; **674**
Vanichseni, Suphak; 971, 986
Vanni, Tazio; 856
Vanobberghen, Fiona; **570**
Vanpouille, Christophe; 304, 304
Var, Susanna R.; 263, 375, 496, **499**
Vardhanabhuti, Saran; **515**
Vargas, Milenka; 491
Vasudevan, Canjeeveram K.; 1016
Vautrin, Audrey; 104LB
Vavro, Cindy L.; **609**
Vaz, Paula M.; 615
Vazquez, Homero; **219**
Vázquez-Castellanos, Jorge; 266
Vecchione, Maria B.; 821
Veldkamp, Peter; 651, 651
Vella, Stefano; 879
Veloso, Valdilea; 1119, 833, 856, 977, 1119
Velu, Vijayakumar; 370, 820
Vemula, SaiVikram; 258, 258
Venet, Alain; 333
Venuto, Charles; 517
Vera, Jaime H.; **477**
Vera, Mar; 266
Verbon, Annelies; 566, 1105
Verdin, Eric; 385
Vergara, Andrea; 845
Verheyen, Jens; **431**, **568**
Vernazza, Pietro L.; 675, **1008**
Veronese, Fulvia; 966LB
Viale, Pier Luigi; 303, 303, 636
Viall, Abigail H.; 1064
Viana, Raquel V.; 985
Viard, Jean-Paul; 334
Vigano, Selena; **53**, **360**
Vila, Anna; 934
Vilchez, Juan Jesus; 196
Villar, Judith; 714
Villegas, Guillermo; **967**
Villinger, Francois; 168, 298LB
Vimeux, Lene; 329
Vincent, Corine; 146
Vinci, Concetta; 442
Vinikoor, Michael; 439
Vinikoor, Michael J.; 445, **808**
Violari, Avy; 35, 36, 930, 939
Visconti, Elena; 495
Vita, Serena; **303**, **303**
Vitomirov, Andrej; **263**, 499
Vittinghoff, Eric; 1017
Vjecha, Michael; 761
Voigt, Esther; 678
Voisin, Dexter; 1006
Vojtech, Lucia; **366**
Vollbrecht, Thomas; **226**
von Andrian, Ulrich H.; 357
von Kalle, Christof; 381
von Massow, Friedrich; 544
von Stockenstrom, Susanne; **382**
Vongrad, Valentina; 199
Vonthanak, Saphonn; 915
Voss, Cindy; 1065
Vrbanac, Vladimir; 357
Vucic, Emily; 802
Vullo, Vincenzo; 303, 296, 303
Vyboh, Kishanda; 534, 534

– W –

Wagh, Kshitij; 346
Wagner, Anjuli D.; 911
Wagner, Gabriel; 219, 492
Wahl, Angela R.; **425**
Wahl, Sharon; 815
Wahome, Elizabeth; 102
Wahome, Rahab; 1078
Wainberg, Mark; 104LB, 251
Wainberg, Mark A.; 591
Waine, Arnold; 1089, 1089
Waja, Ziyaad; 822, 872
Wakefield, Steven F.; **6**
Walawander, Ann; 451
Wald, Anna; 27
Waldenstrom, Jesper; 664
Walensky, Rochelle P.; 93
Walensky, Rochelle; 1104, 1119, 1104, 1119
Walits, Emily; 599
Walker, Bruce D.; 53
Walker, Bruce; 185, 227, 228, 339, 359
Walker, Bruce D.; 360
Walker, Bruce; 362
Walker, Joshua A.; **753**
Walker, Naomi F.; **811**
Walker, Sarah; 57, 119, 457, 552, 595, 927, 941
Walker-Bone, Karen; 768
Walker-Sperling, Victoria; 427, **393**, 427
Wallace, Danelle; 661
Wallis, Carole L.; 985
Walmsley, Sharon; 777
Walsh, Terri; 995
Walusansa, Victoria; 88
Wamalwa, Dalton; 889, 911, 945, 946
Wan, Yanmin; 324
Wandeler, Gilles; 103LB, 150, 563, 807, 808
Wang, Charlene; 386
Wang, Chia; 147
Wang, Chin-Tien; 235
Wang, Cuiwei; 858, 858
Wang, Gary; 686
Wang, Jaang-Jiun; 235
Wang, Jiajia; 892, 894
Wang, Jian; 523
Wang, Jianbin; 433
Wang, Jing; 581
Wang, Keyun; 50
Wang, Ling; 599
Wang, Ping; 538
Wang, Shelley; 434
Wang, Sheng-Fan; 235
Wang, Shuqi; 421LB
Wang, Xinyue; 903
Wang, Xun; 847
Wang, Yuge; **355**
Wang, Zhengyan; **599**
Wanga, Valentine; **517**
Wanyenze, Rhoda; 1039
Ward, Doug; 997
Ward, John W.; 145
Ware, Norma C.; 1075
Warrier, Ranjit; 169
Warszawski, Josiane; 334, **867**
Wasilewski, Lisa; 685
Wasinrapee, Punneeporn; 986
Wasserman, Scott; 731
Watkins, David I.; 361
Watkins, Simon; 188, 188
Watson, Birgit; 117
Watson, Douglas; 396
Watters, Sarah; 35
Watters, Sarah A.; **399**
Watts, Heather; 858, 858
Wavamunno, Priscilla; 37, 927
Wawer, Maria J.; 28, 30, 1084, 1088, 158, 452, 453, 454, 458, 1084, 1085, 1088
Webb, Emily L.; 634
Webb, Kristofor; 309
Webel, Allison R.; 745
Weber, Jacqueline; 165
Weber, Kathleen M.; 1050
Weber, Rainer; 582, 805
Weber, Shannon; 25
Webster, Daniel; 377
Webster-Cyriaque, Jennifer; 716
Wechsberg, Wendee M.; **852**
Wei, Jeffrey; 136
Wei, Stanley C.; 747, 747
Wei, Xuelian; 951
Wei, Ying; 1036
Weimar, Katja; 614
Weinberg, Ethan M.; 644, 644
Weinreb, Caleb; 1116
Weinstein, Milton; 1104, 1104
Weinstock, Hillard S.; 839
Weintrob, Amy; 847
Weis, Julie F.; **983**
Weis, Nina; 877
Weiser, John; 974
Weissman, Drew; 810
Wejnert, Cyprian; 1060, **1041**, 1060
Wellington, Maureen; 118, 574
Welte, Alex; **626**, **616**, **626**
Wendel, Sarah; 869
Wendling, Marie-Josée; 701
Wensing, Annemarie; 229
Wensing, Annemarie M.; 243
Wensing, Annemarie; 549
Were, Edwin; 980
Werner, Barbara G.; 613
Werner, Lise; 984
Wertheim, Heiman; 843
Wertheim, Joel O.; **120**, **239**
Wertheim, Joel; 241
Wertheim, Joel O.; 242, 246
Wertheim, Joel; 600
Wesolowski, Laura G.; 613, 621
West, Nora; 895
Wester, C. William; 558
Wester, William C.; 990
Westergaard, Ryan P.; 783
Westerman, Larry; 631
Westfall, Andrew; 1004
Westheimer, Emily; 620, **1069**
Westlake, Christopher J.; 45
Westmacott, Garrett; 287
Weyant, Christopher; 1121
Wheeler, Amber L.; 770
Wheeler, Darrell P.; 116, 1017
Wherry, E. John; **172**, 656
White, Cory H.; **409**, 424
White, Ellen; **596**
White, Kirsten L.; 605, 952

White, Laura F.; 217
Whitehead, Sara; 855
Whitney, James B.; **108**
Wiboonchutikul, Surasak; **957**, **957**
Wichukchinda, Nuanjun; 275, 276
Widenfelt, Erik V.; 990
Widera, Marek; 431
Wiedemann, Aurelie; 819
Wiegand, Ann; 106
Wieland, Amanda; 652
Wierman, Margaret; 859, 859
Wiertz, Emmanuel J.; 403
Wiesner, Lubbe; 555
Wietgrefe, Stephen; 416
Wiewel, Ellen W.; 99
Wightman, Fiona; 358
Wilkerson, Gregory; 223
Wilkin, Timothy J.; **710**
Wilkinson, Eduan; 256, 248, 256, 603
Wilkinson, Katalin A.; 811
Wilkinson, Robert J.; 835, 811, 835
Willberg, Chris; 111LB
Williams, Brett; 319
Williams, Brian; 1112
Williams, Darlisha; 836, 838, 826, 836, 838
Williams, Deborah; 794
Williams, James; 111LB
Williams, Julie C.; 183
Williams, Kenneth C.; 753
Williams, Paige L.; 882, 917, 936, 944
Williams, Peter E.; 554LB
Williams, Sophie; 89
Williams, Tiffany; 632LB
Williamson, Anna-Lise; 314
Wilson, Cara C.; 186, 262, 763
Wilson, David; **75**
Wilson, Eleanor M.; 302, 302, 311, **683**
Wilson, Kate S.; **853**
Wilson, Wyndham; 399
Winkler, Cheryl A.; 197
Winkler, Cheryl; 933
Winston, Alan; 472, 477
Winters, Mark A.; 708LB
Wirth, Nathalie; 139
Wiseman, Roger; 363
Wisnivesky, Juan; 715
Wit, Ferdinand W.; 472, 806
Witkowska, H. Ewa; 208, 209
Witt, Mallory; 743
Witte, John S.; 295
Witte, Torsten; 282, 297
Witten, Jade; 455
Wittkopp, Cristina; **194**
Woelk, Christopher H.; 407, 408, 409, 424
Wohl, David; **113LB**
Wohlfeiler, Michael; **577**
Wohlschläger, Jeremias; 568
Wolbers, Marcel; 843
Wolf, Elizabeth; 250
Wolff, Eva; 568
Wolff, Marcelo J.; 430
Wolinsky, Steven; 288
Wolter, Franziska; 678, 680
Wolters, Femke; 403
Womack, Julie; 141
Wong, Alexander; **598**
Wong, Cherise; 1053
Wong, Dean; 482
Wong, Joseph K.; 210
Wong, Kimberly; 138
Wong, Michael; 799
Wong, Queenie; 777
Wong, Wing-Wai; 235
Wood, Lianna F.; **897**
Wood, Robin; 559
Woodd, Susannah; 762
Woods, Steven; 450
Woods, Steven P.; 491, 496
Woodward, Mark; 648, 648
Wook-Chun, Tae; 267, 547
Wools-Kaloustian, Kara; 563
Wortley, Pascale M.; 1064
Wright, Alicia; 827LB
Wright, Patrick W.; **60**
Wringe, Alison; 570
Wroe, Emily B.; 721
Wu, Alan; 757
Wu, Fan; 503
Wu, Hao; 56, 444
Wu, Hsiu; **1018**
Wu, Julia W.; **612**, **612**
Wu, Xiaolin; 105
Wu, Xingye; 824
Wu, Xueling; 344
Wu, Yufan; 351
Wyatt, Christina; 981
Wyles, David; **147**, **151LB**, 661, 691
Wynn, Bridget; 925
Wynne, Brian; 550
Wyvill, Kathleen M.; 87

– X –

Xia, Qiang; 99
Xia, Weibo; 790
Xiao, Hong; 114LB
Xiong, Yong; 228
Xu, Cuiling; 406, 965

– Y –

Yadav, Anjana; 502
Yalamanchili, Rachana; 149, 648, 648
Yamaguchi, Julie; 257, 257
Yamamoto, Takuya; 394
Yan, Isabel; 832
Yan, Peng; 643
Yang, Bin; 1096
Yang, Chia-Jui; 235
Yang, Chunfu; 615
Yang, Hongbing; 377
Yang, Jenny C.; 152LB
Yang, Lifei; **348**
Yang, Ligang; 1096
Yang, Otto O.; 289, 365
Yang, Wan-Lin; 244
Yang, Zhiyuan; 202, 202
Yanik, Elizabeth L.; **725**, **725**
Yarchoan, Robert; 87, 399
Yasunami, Michio; 275, 276
Yates, Nicole; 905
Yatich, Nelly; 800, 1081
Yazdanpanah, Yazdan; 891, 1009, 1122
Ye, Diarra; 512
Ye, Weiguo; 482
Yebra, Gonzalo; **236**
Yee, Ka Lai; **521**
Yee Kien, Chong; 820
Yeh, Wendy W.; **522**
Yehia, Baligh R.; 890, 996
Yek, Christina C.; **391**, **391**, **492**
Yende, Nompumelelo; 895
Yeo, Anthony E.; 145
Yerly, Sabine; 244, 245, 253, 377
Yi, Guohua; **356**
Yin, Michael T.; **141**, 143LB, 787, 932
Yin, Michael T; 780, 770, 775, 780, 790
Yin, Philip; 687, 688
Ying, Roger; **1106**, **1112**
Yoh, Sunnie M.; **43**
Yonaba, Caroline; 512
Yong, Michelle K.; **281**
Yong, Patrick; 392, 392
Yoshimura, Kazuhisa; 590
Yoshinaga, Noriyoshi; **200**
Yoshioka, Hirofumi; 402
Younan, Patrick; 401
Young, A. Toni; 665
Young, Benjamin; 997
Young, Lindsay; 1006, 1070
Young, Mary A.; 858, 294, 516, 676, 775, 792, 858
Young, Sean D; 1098
Yu, Chunjiang; 478, 507
Yu, Chunli; 880
Yu, Di; 358
Yu, Nancy; 1054
Yu, Xin; 56
Yu, Xu G.; 53
Yu, Xu; 185
Yu, Xu G.; 360
Yucha, Robert W.; **421LB**
Yue, Ling; 364
Yueh, Yun Lan; 966LB
Yuen, Tracy; 469
Yuhas, Krista; 853
Yukl, Steven; 210
Yurchenko, Alexander; 1042
Yurick, David; 412
Yuste, eloisa; 347
Yutthakasemsunt, Naruepon; 788

– Z –

Zaba, Basia; 570, 583, 1046
Zablotska, Iryna B.; 1019LB
Zaccarelli, Mauro; 63
Zacchi, Fabio; 655
Zahnd, Cindy; **150**, 675
Zaidi, Akbar A.; 839
Zakhour, Ramia; **922**
Zaki, Sherif; 862
Zako, Linda; 830
Zamborlini, Alessia; 540
Zanchetta, Marisa; 923
Zangerle, Robert; 602
Zash, Rebecca; **871**, **878**
Zayyad, Zaina; **475**
Zeh, Clement; **625**, 624, **625**, 632LB
Zeldis, Jerome B.; 87
Zeng, Hui; 444
Zentner, Isaac; **195**
Zerbato, Jennifer M.; **423**
Zerbe, Allison; 864, 864
Zerbe, Allison V.; 888, **1103**
Zetterberg, Henrik; 59, 60, 62, 470, 473, 474
Zhang, Fujie; 56, 444
Zhang, Gang; 543
Zhang, Guangxiang G.; 480, 754
Zhang, Hongyi; 596
Zhang, Jinbing; 748, 748, 749LB
Zhang, Liguo; 225
Zhang, Lily; 352
Zhang, Long; 489
Zhang, Weiyu; 44
Zhang, Wendy; 697, 1055
Zhang, Xianfeng; 224LB
Zhang, Xiang; 698
Zhao, Hongxin; 56, 444
Zhao, Jiangqin; 258, 258
Zheng, Heping; 1096
Zheng, Jia-Hua; 83, 525, 526
Zheng, Yonghui; **224LB**
ZHENG, Yi; 512
Zhou, Jingling; 320
Zhou, Tao; 224LB
Zhou, Yun; 482
Zhu, Li; 509
Zhu, Ting; 790
Zidar, David A.; 298LB
Ziemniak, Carrie; 33, 374, 396
Zimmer, Bonnie; 939
Zimmerman, Regina; 729
Zimulinda, Eugene; 1087, 1087
Zingman, Barry S.; 29, 1095
Zink, M. Christine; 416
Zinski, Anne; 101, 1004
Zirafi, Onofrio; 208
Zivich, Steven; 668
Zola, Musimar; 718
Zorowitz, Sam; 1063, 1063
Zorrilla, C; 893
Zoulim, Fabien; 706
Zucman, David; 139
Zule, William A.; 852
Zulu, Fatima; **1047**
Zwank, Claudia; 679
Zydowsky, Thomas; 967, 968
Zziwa, Godfrey; 815

KEYWORD INDEX

12-week use; 524
2-LTR circles; 374
2B4; 389LB
3TC; 863, 863
4E10 epitope; 356
4th-generation immunoassay; 613, 620

– A –

Abacavir; 735, 736, 749LB, 782
Abortive infection; 202
Abstinence; 160
ACA; 1066
Acceptability; 955
Access to care; 1066, 1078
Accessory proteins; 123
Acetylation; 404
Acquired drug resistance; 553, 607
Acquired immunodeficiency syndrome; 297
Activation; 321
Acute
- HIV; 47, 48, 272, 305, 359, 438, 473, 841, 961, 961, 1003, 1007, 1116, 1021, 1043, 1044, 1069
- Hepatitis C; 669, 670, 671, 674, 678
- Infection; 218, 364, 613, 620, 702, 866
- Myocardial infarction; 746
- Virus; 215

Acylcarnitines; 498, 880
Acylguanidines; 536
Adeno-associated virus; 163, 400
Adherence; 83, 117, 294, 514, 546, 557, 560, 692, 694, 827LB, 853, 875, 886, 887, 888, 907, 975, 976, 977, 979, 980, 990, 992LB
Adipokine; 770
Adipose tissue; 744
Administrative data; 1054
Adolescents; 241, 250, 450, 918, 943, 944, 950, 952, 953
Adults; 115LB, 462, 628, 1076
Adverse events; 829
Advocacy; 6
Africa; 37, 57, 88, 154, 622, 544, 552, 555, 573, 622, 629, 722, 764, 793, 809, 907, 929, 941, 969, 1014, 1034, 1059, 1078, 1079
African; 808, 933
African American; 850
Age; 742
Aging; 84, 306, 307, 485, 492, 495, 499, 506, 725, 741, 783, 785, 786, 881, 923, 1053
Agonistic antibody; 358
AIDS; 308, 496, 1104
- Diagnoses rates; 999
- Events; 562
- Indicator survey; 1037

AIDS-free survival; 1009
AIDS-related malignancy; 69
Albuminuria; 796
Alcohol; 639, 804, 808, 852, 925, 1005, 1036, 1037, 1038, 1050
Alere PIMA; 632LB
Alere q; 34
Algorithm; 633
Allelic exclusion; 277
Allograft rejection; 798
Allometry; 949
Allo SCT; 431
Allosteric inhibitor; 540
Alpha 4 beta 7; 217
ALVAC/AIDSVAX; 166
Amyloid; 208, 209, 482, 483
Anaerobes; 1085
Anal cancer; 90, 715
Anal swabs; 568
Analytic treatment interruption (ATI); 352, 378, 434
Anatomic compartments; 435, 525
Ancestry; 933
Anergy; 284
Angiographic restenosis; 730
Anthropometric; 762
Anti-HB antibody seroconversion; 703
Anti-HBs antibodies; 701
Anti-HBs titers; 700
Anti-PD-L1; 371
Antibodies; 64, 163, 170LB, 834, 259, 340, 589, 834, 903, 905
Antibody response; 430, 987
Antibody-dependent cell-mediated cytotoxicity (ADCC); 162
Antidiabetics; 531
Antigen-specific responses; 330
Antigen/antibody assays; 618
Antiretroviral; 33, 38LB, 57, 142, 451, 513, 519, 522, 540, 555, 574, 793, 882, 886, 896, 1079, 1114
- Drug; 116, 265, 444, 818
- Drug transporters; 534, 534
- Failure; 606
- Nanomedicine; 528
- Pharmacokinetics; 83, 84, 509, 525
- Tissue penetration; 548
- Treatment; 1118

Antiretroviral therapy (ART); 29, 35, 36, 56, 88, 108, 155, 157, 159, 161, 297, 305, 322, 332, 396, 343, 376, 389LB, 435, 436, 445, 450, 466, 546, 557, 559, 563, 565, 570, 576, 578, 579, 580, 583, 584, 597, 600, 615, 638, 720, 721, 738, 739, 805, 808, 810, 832, 835, 837, 853, 864, 865, 866, 875, 887, 888, 913, 915, 920, 929, 945, 946, 984, 989, 990, 997, 998, 1001, 1011, 1012, 1023, 1056, 1059, 1077, 1080, 1084, 1094, 1095, 1106, 1110, 1112, 1119, 1120
- Adherence; 8
- Care evaluation; 561
- Cascade; 1008
- Coverage; 535, 1064
- Initiation; 270, 575, 778, 836, 1001, 1007, 1012, 1081, 1112
- Intensification; 271
- Naive; 780
- Outcomes; 155, 566
- Patients; 381
- Program monitoring; 561
- Scale-up; 159, 1071
- Switch; 118, 733

Antituberculosis treatment; 95LB
Antiviral activity; 114LB, 287, 527
Antiviral immune response; 569
Antiviral therapy; 656
Aorta; 753
APOBEC3; 194
APOBEC3G/F; 193
APOE; 463
APOL1; 933
APOL6; 191, 191
Apoptosis; 387, 411
Aqueous humor; 848
ARS; 1044
Arterial inflammation; 738
Arterial stiffness; 925
Asia; 915
Asian; 703
Assay; 91, 612
Astrocyte; 473, 478, 507, 508
Asunaprevir; 146, 683, 687, 688
Asymmetric dimethylarginine (ADMA); 758
Asymptomatic neurocognitive impairment; 465
Atazanavir; 515, 794
Atazanavir/ritonavir; 520
Atherosclerosis; 136, 752, 755, 926
Atorvastatin; 136
Atorvastatin adjunct therapy; 322
Atovaquone; 520
Atripla; 871, 878
Attachment inhibitor; 509, 523, 545
Attributable; 1038
Attrition; 881
ATV/r monotherapy; 442, 443, 773
Autologous HIV-1; 199
Autologous stem cell transplantation; 429
Autophagy; 395, 410
Autophagy-related protein 7; 410
Autopsy; 825
Avidity; 623, 1042
Awareness; 1014
Azithromycin; 845

– B –

B cell follicle; 370
B cell responses; 342
B cells; 166, 339, 340, 341
Bacillary load; 819
Bacterial functions; 260
Bacterial vaginosis; 861
Balance; 786
BCG; 279, 948
Bcl-2; 411
Behavioral; 74
Beta catenin; 507
Bias; 1030
Bifurcation; 754
Bio-rad avidity enzyme immunoassay; 625, 625
Biodegradable; 542
Bioenergetics; 497
Bioinformatics; 13, 261
Biologic measure; 1030

Biomarker; 110LB, 302, 308, 309, 449, 471, 479, 483, 485, 565, 927
Birth; 910
- Cohort; 145
- Outcomes; 878
- PCR; 34

Bispecific antibodies; 167
Black; 116, 839
Black MSM; 1006
Blimp-1; 341
Blood donation; 1010
Blood safety; 1010
Blood tested; 555
BMS-626529; 509, 523, 545
BMS-663068; 509, 523, 545
BMS-791325; 687, 688
BMS-955176; 114LB
BMS-986001; 541
BnAb; 49
Body composition; 770, 779, 930
Bone; 769LB, 775, 932
- Biomarkers; 766, 773, 777
- Disease; 765, 772, 776
- Marrow; 340
- Metabolism dysfunction; 791
- Turnover markers; 790, 879

Bone and renal safety; 143LB, 795, 953
Bone mineral density (BMD); 143LB, 780, 766, 767, 768, 770, 771, 773, 774,
776, 777, 780, 931
Botswana; 870, 876, 990
Brain; 416, 436, 485, 490
Brain structure; 494
Branch-chain amino acids; 880
Brazil; 1119, 1119
Breast milk; 884, 903
Breast-milk transmission; 897
Breastfeeding; 33, 886
Broad neutralization; 351
Broadly neutralizing antibodies; 165, 343, 344, 346, 356, 685
BST-2/Tetherin; 503
Burden; 1055
Burden of disease; 145
Burkina Faso; 236
Bystander pathogenesis; 327

– C –

Cabotegravir; 554LB, 966LB
Calcified plaque; 138
Calcineurin inhibitors; 798
Calibration; 141
Cancer; 105, 718, 724, 741
Cancer risk; 725
Cancer survival; 715
Cape Town; 978LB
Capsid; 184, 184
Cardiometabolic health; 745
Cardiovascular; 37, 319, 748, 753, 882
Cardiovascular disease; 134, 138, 747, 751, 655, 729, 730, 734, 741, 742, 747, 751, 756, 781, 925, 928
Cardiovascular disease risk factors; 487, 733, 734, 739, 744, 751, 759, 782, 749LB, 757, 782
Care; 1000
Care-delivery model; 1091
Care retention; 1009
Caribbean; 1078
Carotid; 137
Carotid intima-media thickness; 754, 925
Carrageenan; 967
cART; 336, 352, 505, 581, 776, 881, 901, 902, 917, 1051
Cascade; 896, 1109
Cascade of care; 32, 659, 666, 973, 1008, 1092
Case control; 1054
Case-control study; 674, 777
Caspase-1; 202
Cause of death; 825
Cause-specific mortality; 579, 583
CCR5; 163, 219, 227, 314, 327, 433, 814, 858, 965
CCR5 delta32 mutation; 431
CCR5 expression; 859
CD127; 820
CD16; 418
CD169/Siglec1; 188, 188, 222
CD31; 922
CD34+ hematopoietic stem cells; 528
CD38; 820
CD4 T cell; 163, 199, 226, 227, 335, 357, 364, 368, 377, 388, 422, 530, 543, 577, 579, 590, 630, 631, 812, 1048
- Count; 315, 332, 551, 570, 582, 611, 728, 806, 913, 921, 924, 1001, 1007, 1081, 1094, 1112, 1117
- Death; 331
- Depletion; 320
- Monitoring; 563, 920
- Nadir; 456
- Receptor; 223
- Reconstitution; 1015
- Recovery; 294, 331, 574
- Response; 569, 819

CD4/CD8 ratio; 728, 267, 306, 318, 335, 728, 741
CD57; 820
CD62L; 426
CD8 suppression; 361
CD8 T cell; 167, 169, 359, 362, 368, 370, 508, 579, 814, 821
CDK; 204, 205
CDR-H3; 355
Cell activation; 204, 205, 549
Cell-associated RNA; 49, 106, 383, 427
Cell death; 311
Cell-to-cell infection; 220
Cell-to-cell transmission; 165, 220, 283
Cellular accumulation; 527
Cellular factors/Cytokines; 297
Cellular restriction; 192
Central America; 1032
Central fat; 140
Central memory T cells; 424
Central nervous system (CNS); 58, 435, 438, 445, 446, 477
Cerebrospinal fluid (CSF); 48, 439, 443, 444, 473, 483, 505
Cerebrospinal fluid viral escape; 443
Cerebrovascular; 760
Cervical cancer; 710, 711, 712
Cervical cancer screening; 89
cGAS; 43, 184, 184, 185
Chains; 248
Chemokine receptor; 274
Chemotherapy; 70, 88, 399, 429, 711, 721
Chest tomography; 727
Childhood tuberculosis; 938
Children; 278, 512, 724, 877, 911, 924, 926, 935, 936, 941, 945, 949, 950
China; 56, 1030
Chlamydia trachomatis; 357
Cholesterol; 737, 750
Cholesterol regulation; 731
Chronic; 1053
Chronic hepatitis B; 720
Chronic hepatitis C; 657, 680, 682, 695, 720
Chronic HIV infection; 437, 438, 796, 866
Chronic Inflammation; 312, 320
Chronic kidney disease; 142, 642, 655, 797
Chronic lung disease; 800
Chronic virus; 215
Circulating recombinant form (CRF); 236
Circumcision; 175
Cirrhosis; 146, 641, 688
CKD; 933
Clearance; 372, 713
Clearance prediction; 949
Cleavage; 539
Clinical
- Assay; 281, 697
- Monitoring; 563
- Outcomes; 921, 984, 1011
- Parameters; 849
- Pharmacology; 526, 838
- Prediction rule; 604
- Trial; 838, 139, 337, 352, 369, 428LB, 691, 838, 951, 953

Clonal expansion; 105, 106, 399
Clonal HIV populations; 382
Cluster; 238, 243
CNS; 61, 440, 449
CNS disease; 476
Codominance; 277
Coevolution; 122, 203, 586
Coinfection; 151LB, 679, 831, 839, 967
Copay; 1067
Coreceptor switch; 219
Coagulation; 315, 736, 761
Cobicistat; 795
Codon-pair bias; 587
Cognition; 488
Cognitive; 497
- Impairment; 453, 459, 463, 479, 484, 494, 495
- Performance; 489, 937
- Reserve; 495
- Screening tools; 472

Cohort; 646
Cohort study; 235, 373, 580, 581, 1065
Coinfection; 479, 636, 647, 662, 884
Colon; 48
Combination nanoparticle; 527, 542
Community treatment; 1008
Community viral load; 153, 991LB
Community based; 661, 1025
Community-based HIV testing and counseling; 1111
Community-based intervention; 249
Community-based screening; 665
Comorbidity; 469, 764
Compartmentalization; 440
Complement activation; 481
Complete; 256
Computational biology; 13
Computer simulation model; 249, 532, 1104, 1121
Condoms; 1060
Consistency in subsets; 562
Contraception; 896, 1107
Contraception failure; 85LB
Control; 293
Controllers; 264
Convenient; 1067
COPD; 802
Cord blood; 432

Coronary artery calcium; 137
Coronary artery disease; 136
Coronary artery plaque; 743, 928
Correlates of protection; 904, 966LB
Cost; 1104, 149, 613, 652, 1065, 1104
Cost-effectiveness; 616, 712, 1105, 1106, 1108, 1109, 1110, 1111, 1113, 1122
Cotrimoxazole; 94, 941
Couples; 1106
CPSF6; 196
Creatinine clearance; 517
CRF; 258
CRF01_AE; 275
CRF07_BC; 235
CRF19_cpx; 338
CRISPR-Cas9; 403
Cross-contamination; 592
Cross-group neutralization; 345
Cross-resistance; 985
Cross-sectional incidence testing; 622, 623, 626,673
Cross-species transmission; 237
Cross-talk CD4+ cells and NK cells; 679
Cryptococcal meningitis; 815, 834, 835, 836, 837, 838
Cryptococcosis; 836, 838Crystallography; 586
CSF; 835
CSF biomarkers; 443, 454, 460
CTL; 363, 406
Cuba; 338
Culture-negative TB; 833
Cumulative CD4; 746
Cumulative risk; 142
Cumulative VACS index; 746
Cumulative viral load; 746
Cure; 6, 104LB
Cutaneous biopsies; 723
CVD; 742
CXCL10; 681
CXCL12/CXCR4-CXCR7; 723
CXCL13; 339
CXCR4; 219, 336
CXCR4 antagonists; 213
CXCR7; 213
CYP2B6; 533
Cystatin C; 484, 934
cytokine; 323, 1085
Cytokines; 289, 310, 329, 454, 480, 848
cytology; 710, 856
Cytolytic; 364
Cytomegalovirus (CMV); 300, 301, 302, 319, 575, 848, 884
- Replication; 304, 375, 1020

Cytotoxic T lymphocytes; 365
Cytotoxicity; 367

– D –

D-dimer; 565, 899
D-drugs; 806
Daclatasvir; 146, 151LB, 650, 683, 687, 688
Dapivirine; 524, 985
DARPin; 351
Darunavir; 551, 588
DBS; 616
DBS VL; 615
ddPCR; 420
Death; 1000
Decentralization; 155, 1075
Decompensation; 648 656
Deep sequencing; 259, 592, 605
Defective provirus; 392
Defensins; 211
Degenerative; 461
Degradation; 40
Dementia; 56, 452, 482, 493
Democratic Republic of Congo; 234
Demographic surveillance; 161, 1102
Dendritic cells; 46LB, 124, 184, 185, 222, 284, 354
Deoxyribonucleotide; 526
Depot medroxyprogesterone acetate (DMPA); 861
Depression; 498, 695, 809
Device acceptability; 1087
DH gene segment; 355
DHEA; 821
Diabetes; 788
Diabetes mellitus; 655, 771, 789
Diagnosis; 130, 628, 635, 661, 1007, 1008
Didanosine; 782
Didehydro-Cortistatin A; 413
Differentiation; 986
Diffuse tensor imaging; 935
Direct transmission; 233
Direct-acting antiviral (DAA); 16, 18, 147, 148, 181, 651, 653, 670, 675, 689, 695
Directly observed therapy (DOT); 828LB
Disclosure; 1004
Discontinuation; 1080
Discordant; 629
Discrimination; 141
Disease progression; 611, 660, 922
Disparity; 581, 1041
Disulfiram; 428LB
Diversity; 230
DNA damage response; 41
DNA methylation; 197, 506, 802
DNA repair; 200
Dolutegravir; 550, 594, 609, 610
Dolutegravir resistance; 121
Donor-to-donor variation; 408
Doravirine; 521
Dose escalation; 428LB
Double dose; 701
Down-referral; 155, 1074
DPP4; 681
Dried blood spots; 83, 514, 617
Droplet digital PCR; 420, 499
Drug; 603
- Combination; 590, 863
- Discovery; 18
- Distribution; 535
- Interactions; 82, 513, 520, 522, 523, 531, 532, 651
- Resistance; 117, 118, 119, 120, 214, 238, 541, 553, 585, 586, 591, 595, 597, 602, 605, 610, 693, 829, 908, 952
- Resistance testing; 91
- Resistance mutations; 686
- Use; 783, 852, 971, 1005, 1006, 1029

Drug-resistant tuberculosis; 92, 130
Dual infection; 347, 232, 233
Dual prevention; 1107
DuoGel; 510
Durability; 653
DXA; 776, 777
Dynamic treatment regimen; 7
Dyslipidemia; 731, 929

– E –

E/C/F/TAF; 113LB
Early
- Antiretroviral therapy (ART); 47, 115LB, 374, 375, 475, 546, 926, 1083, 1091, 1095
- cART; 446, 473
- Diagnosis; 727
- HIV infection; 47, 48, 51, 1007, 1116, 1021
- Infant antiretroviral therapy; 912
- Infant diagnosis; 34, 873, 874
- Loss; 1080
- Samples; 236

East Africa; 1056, 1072
Ebola; 76, 77
Ebola epidemic; 103LB
Economic evaluation; 1108
Economic restoration; 1056
Education; 658
Efavirenz; 38LB, 84, 85LB, 448, 500, 520, 531, 533, 535, 737
EFdA; 537, 585
Effectiveness; 950, 1088
Effector function; 64
Effector/memory; 821
Efficacy; 545, 844, 954
eGFR; 742
eGFR reversibility; 981
Electrocautery; 714
Electronic medical records; 668
Elite controller; 227, 332, 427
Elite suppressor; 393, 427
Elvitegravir; 113LB, 795, 951, 952
Emergence; 237
Emergency department; 98, 667, 1100, 1113
Emphysema; 802
Emtricitabine; 23LB
End-stage liver disease; 638, 657
Endgame; 244
Endoribonuclease; 402
Endothelial dysfunction; 298LB
Endothelial function; 732, 737, 757, 759
Endothelium; 475
Engagement in care; 154, 970, 1000, 1080, 1092
eNOS; 298LB
Entropy; 612
Entry inhibition; 351, 350, 590
Env; 224LB
Envelope; 217, 259, 355
Envelope trimer; 39, 216
Epidemiology; 9, 73, 99, 127, 135, 153, 229, 238, 249, 253, 256, 493, 717, 724, 725, 846, 867, 1011, 1057, 1118
Epigenetics; 413, 506
Epithelial cells; 802
Epitope; 355
Epstein-Barr virus; 69
Eradication; 387, 403, 432, 535, 657
ERCHIVES; 642, 643
Error correction; 592
Escape; 364
ESLD; 799
ESRD; 799
Estrogen; 859, 859
etravirine; 892, 893
Etravirine and darunavir/ritonavir; 523
Europe; 1008
Evolution; 120, 194, 230, 239, 248, 254, 587, 686
EWAS; 197
Ex vivo models; 964
Ex vivo; 202
Executive function; 488, 936
Exercise; 488
Exhaustion; 111LB, 300

Exosomes; 366
Explant; 86LB, 968
Exposed seronegative; 290
External validity; 578

– F –

Facility factors; 1072
FACTS; 26LB
Failure; 699
Falls; 786
False-negative; 635
False-recent rate; 625
Fc fusion; 350
Female and male; 921
Female condom; 995
Female reproductive tract; 273
Female sex workers; 135, 851, 852, 861
Fetal; 882
Fetus; 898
Fever; 883
Fibrosis; 150, 299LB, 325, 639, 643, 656
Financial incentives; 29
Financing; 1114
First-line ART failure; 457
Fishing communities; 1039
Fixed-dose combination; 687, 688
Flow cytometry; 680
Flow-mediated dilatation; 757
Food insecurity; 546
Foxo1; 426
Fozivudine; 544
Fraction; 1038
Fracture; 141, 775, 777
Frailty; 783
FRAX; 141
Functional HIV cure; 401
Functionality; 995
Fungal burden; 835
Fungal infection; 843
Fusion inhibitors; 589

– G –

Gag; 276, 328, 539
GALT; 263, 547, 548
Gamma delta T cell; 278
Gender; 581
Gene editing; 400, 401, 434
Gene expression; 405, 408, 802
Gene therapy; 365, 400, 401, 402, 403, 434
Gene transfer; 66
Generalizability; 578
Genetic diversity; 242
Genetic polymorphisms; 697
Genetic variant; 461
Genetics; 293, 295, 516
Genital; 855
Genital tract HIV RNA; 857
Genital tract sampling; 857
Genome; 256
Genome-wide association; 517
Genomics; 293
Genotype; 662, 664, 856
Gentian violet (GV); 844
Geographic differences; 996
Germinal center; 49, 167, 326
GFR; 642
GHESKIO; 156
Gift voucher intervention; 1102
Global; 38LB
Global deficit score; 478
Glucose metabolism; 320
Glycolysis; 497
Glycosylation; 215, 350
gp120; 212
gp120 transgenic mouse; 481
gp41 cytoplasmic tail; 220, 503
gp41 mutants; 589
Griffithsin/carrageenan; 968
Group O; 230
Growth; 879
GSK1265744; 554LB
GSK2838232; 538
GSS; 117
Guidelines; 99, 974, 1079, 1081
Gut; 270
- Associated lymphoid tissue (GALT); 271, 299LB
- Homing; 274
- Immunology; 271
- Metagenome; 260
- Microbiome; 262
- Microbiota; 138, 261, 264, 265

GWAS; 295

– H –

HA; 210
HAART; 71, 315
Hair concentrations; 514
Half-life; 81
HAND; 440, 452, 453, 464, 468, 471, 474, 482, 487, 500, 502
Harm reduction; 1063
HBsAg seroconversion; 703
HBV; 700, 702
HCV; 146, 149, 636, 639, 642, 644, 646, 647, 652, 658, 668, 675, 690, 696, 699, 1010
- Antibody avidity; 673
- NS3; 697
- Sequence; 664
- Testing; 665, 667, 668
- Treatment; 670

HCV/HIV coinfection; 147, 522, 653, 691
HDACi; 109, 369, 405, 422
Health
- Care reform; 1066
- Policy; 1119
- Systems strengthening; 159
- Care personnel; 1027
- Care providers; 658, 1083, 1095

Healthy aging; 484
Hearing loss; 829
Helicobacter pylori; 849
Hematopoietic stem cells; 433
Heme oxygenase-1; 501, 502
Hemophilia; 690
Hepatitis; 807
Hepatitis B; 662, 701
Hepatitis B virus; 638, 706
Hepatitis C; 15, 18, 150, 180, 181, 648, 649, 651, 653, 654, 660, 661, 662, 672, 676, 681, 684, 686, 694, 1029
- Treatment; 660
- Virus; 79, 145, 486, 638, 641, 650, 666, 673, 693
- Virus incidence; 660
- Virus kinetics; 683
- Virus treatment; 659, 669
- Virus vaccine; 685

Hepatitis D; 707
Hepatitis delta; 708LB
Hepatocellular carcinoma; 150, 640, 643
Heritability; 291
Herpes simplex virus; 27
Herpes virus coinfection; 190
Heterogeneity; 11
Heterosexual; 1031
Heterosexual women; 978LB
HEV; 709
HEV RNA; 709
High-dose rifampin; 95LB
High Mobility Group Box 1; 722
High-grade anal intraepithelial neoplasia; 714
High-mannose glycan; 350
Highly exposed seronegative; 288
Histone acetylation; 407
Histone deacetylase inhibitor; 408, 410, 411
Histone methylation; 407
Histopathology; 464
HIV; 37, 56, 59, 79, 84, 86LB, 90, 107, 134, 136, 146, 160, 162, 170LB, 192, 207, 248, 256, 273, 282, 290, 296, 299LB, 301, 306, 316, 319, 323, 342, 353, 360, 371, 394, 403, 412, 432, 445, 452, 462, 463, 471, 482, 486, 493, 502, 505, 507, 512, 520, 537, 549, 557, 573, 575, 580, 599, 617, 623, 628, 629, 634, 635, 639, 646, 647, 707, 709, 713, 716, 722, 730, 731, 740, 743, 748, 753, 756, 757, 774, 775, 783, 798, 801, 805, 808, 809, 815, 831, 833, 842, 846, 867, 868, 890, 891, 893, 901, 903, 905, 906, 911, 927, 944, 945, 954, 958, 974, 992LB, 1002, 1010, 1014, 1017, 1026, 1029, 1032, 1034, 1038, 1040, 1049, 1050, 1052, 1055, 1057, 1074, 1081, 1082, 1096, 1098, 1103, 1104, 1113
- Adherence; 988
- Cancer risk; 725, 717, 718, 725
- Associated neurocognitive disorder; 62, 63, 446, 447, 454, 456, 472, 483, 489, 493, 501, 506
- Associated neurocognitive impairment; 444, 478
- Associated non-AIDS; 565
- Care; 103LB
- Care cascade; 252, 632LB, 1003, 1111
- Care continuum; 665, 851, 854, 890, 973, 997, 1005, 1068, 1097
- Cluster; 598
- Coinfection; 819, 849
- Controllers; 333
- Counselling; 177
- Cure; 417
- Dementia; 453, 455
- Dementia scale; 459, 472
- Diagnosis; 1061
- Diagnostic algorithm; 613
- Disease progression; 97
- DNA; 61, 429, 437, 480, 568
- DNA decay; 374, 375
- DNA reservoir; 58, 435, 491, 492
- Drug resistance; 116, 594, 601, 604, 606, 607, 907, 982, 983
- Encephalitis; 481
- Entry; 39, 212
- Epidemic; 1045
- Eradication; 61, 108
- Exposed; 880
- Exposed infants; 889
- Exposed uninfected children; 876, 881
- Expression; 390, 106, 390
- Immunology; 295

- Incidence; 22LB, 626, 625, 624, 625, 626, 991LB, 1046, 1042, 1047, 1117
- Infected children and adolescents; 78
- Infected patients; 381
- Infection; 139, 197, 210, 640, 750, 767, 784, 788, 824, 844, 957, 1033, 1039
- Interventions; 176
- Latency; 61, 388, 407, 408, 409, 424
- Malignancies; 71
- Mortality; 1076
- Pathogenesis; 302
- Persistence; 108, 109, 267, 386, 396
- Positive children; 915, 929
- Positive unaware; 1070
- Prevention; 6, 20, 25, 241, 252, 895, 970, 972, 975, 981, 982, 1039
- Production; 549
- Provirus; 379
- Recent (early) infection; 244
- Replication control; 52, 328
- Reservoir; 106, 168, 373, 376, 378, 382, 383, 386, 390, 399, 429, 430, 535
- Restriction and host factors; 189
- Risk; 1028, 1062
- RNA; 568
- RNA suppression; 920
- Self-testing; 1098
- Serodiscordant couples; 988, 989, 1019LB
- Shedding; 30
- Status; 715, 1037
- Subtype; 594, 1044
- Surveillance; 99, 1092
- Surveillance data; 665, 854
- Susceptibility; 860
- Testing; 98, 177, 614, 1013, 1018, 1071, 1073, 1099, 1100, 1101
- Transmission; 54LB, 211, 218, 252, 289, 404, 1020, 1095, 1121
- Transmission clusters; 241, 242
- Transmission Linkage; 240, 244, 1035
- Treatment as prevention; 127, 1019LB
- Treatment cascade; 154, 852
- Tropism; 221, 431
- Vaccine; 166
- Viral evolution; 492
- Viral load; 865, 582, 865, 924, 997, 1112

HIV-1; 28, 35, 40, 43, 45, 46LB, 117, 118, 165, 183, 185, 189, 195, 196, 214, 220, 230, 235, 247, 261, 262, 352, 399, 404, 423, 434, 470, 539, 543, 550, 554LB, 574, 585, 600, 614, 615, 621, 633, 834, 870, 898, 916, 919, 933, 950, 988, 1084, 1089

- Cell-associated RNA; 912
- Diversity; 231
- DNA; 377
- Env; 327
- Eradication; 391
- Evolution; 41
- Gag epitopes; 365
- gp120; 327
- Infection inhibition; 213
- Infection phenotypes; 261
- Inhibition; 967
- Integrase; 121, 610
- Integration; 198
- Latency; 368, 369, 393, 415, 417, 419
- M/O recombinant; 233
- Mouse model; 528
- Neutralization; 589
- Persistence; 380, 420
- Protease; 586
- Reactivation; 398
- Reservoir; 35, 380, 398, 417, 422
- RNA; 48
- Single-copy assay; 912
- Specific T cells; 377
- Subtype C; 54LB
- Subtypes; 234
- Subtyping; 258
- Transmission; 251
- Unspliced RNA; 384
- Vaccine; 348, 356
- Viral load; 866
- Vpu; 536

HIV-2; 222, 541, 576, 588, 614, 621
HIV-associated neurocognitive disorders (HAND); 437, 441, 450, 461, 464, 465, 466, 480, 492
HIV-exposed; 883
HIV-exposed children; 885
HIV-exposed infants; 884
HIV-exposed uninfected; 289, 877
HIV-infected; 780
HIV-infected adults; 155, 570, 747
HIV-infected children; 35, 36, 513, 920, 939, 956
HIV-infected infants; 884
HIV-infected men who have sex with men; 672, 674
HIV-infected population; 845
HIV-M; 232
HIV-O; 232
HIV-specific CD8 T cells; 53, 369
HIV/AIDS; 458, 558, 843
HIV/CMV coinfection; 303
HIV/HBV coinfection; 703, 704, 705
HIV/HCV Coinfection; 152LB, 598, 637, 645, 649, 651, 654, 655, 659, 677, 678, 680, 683, 689, 692, 695, 698, 942
HIV/TB Coinfection; 93, 820, 830
HIV+NSG-HuPBMC mice; 508
HLA; 275, 276, 293, 362
HLA alleles; 328, 924
HLA class I; 228
HLA-associated polymorphisms; 328
HLA-G; 360
HMGB1; 285, 722
Home HIV testing; 1102
Home HIV testing and counseling; 1090, 1111
Home testing; 1097
Homocysteine; 470
Honduras; 607
Hormonal contraception; 858
Hospitalizations; 783, 877
Host factors; 195, 197
Host genetics; 291, 294, 460, 515
Host restriction factors; 386
Host-pathogen interaction; 123
Host-virus interactions; 41
Hotspots; 199
Household contacts; 817
HPV; 90, 568, 710, 716, 856
HSCs; 207
HSIL; 90
HSV-2; 28, 855, 1084
HSV-2 inhibition; 967
HTLV-1; 214
Human herpesvirus 8; 87
Human ICAM-1 transgenic mice; 356
Human immunodeficiency virus; 410
Human papillomavirus; 713, 943
Human rhinovirus; 356
Humanized mice; 368, 543, 677
Humans; 279
Humoral immunity; 430, 834
Humoral response; 237
HVTN505; 55LB
Hydroxymethylglutaryl-CoA reductase inhibitors; 750
Hypercholesterolemia; 733
Hyperparathyroidism; 791
Hypertension; 739, 740

– I –

ICAM-1; 735
IDU; 1028, 1121
IFITM; 189
IFITM3; 190
IFN; 185
IFN-a; 285
IFN-alpha; 367
IFN-g; 678
IFN-g secretion; 679
IFNOE±; 283
IgG; 709
IL-1; 311
IL-6; 752
IL-10; 311
IL-12/IL-15; 678
IL-18; 313
IL-23; 329
IL-27; 301, 301
IL-32; 296
IL-7; 337
IL1-alpha; 464
Illegitimate integrations; 381
Illumina MiSeq; 261, 592
Imaging; 756, 1089
Immigrant; 1078
Immune; 321

- Activation; 59, 168, 183, 188, 268, 281, 305, 311, 313, 314, 318, 320, 322, 330, 333, 415, 683, 684, 752, 756, 797, 849, 900
- Checkpoint; 388
- Exhaustion; 330, 849
- Recovery; 914
- Reconstitution; 335, 818
- Recovery; 548, 1015
- Response; 393, 466, 815, 986
- Restoration; 575
- Senescence; 305, 923

Immune reconstitution inflammatory syndrome (IRIS); 308, 309, 310, 311, 810, 811, 812, 813, 814, 815, 836
Immunodiscordant individuals; 331
Immunogenicity; 348
Immunohistochemistry; 298LB
Immunologic

- Biomarker; 317
- Failure; 570
- Progression; 333
- Response; 315, 572, 576

Immunology; 273
Immunomodulation; 87, 405, 821
Immunoprophylaxis; 66
Immunosenescence; 820
Immunotherapy; 50, 337
Impact evaluation; 158
Implementation science; 7, 20, 721, 1113
In vitro; 211, 519, 785
In vivo; 425

Incidence; 157, 254, 612, 709, 831, 841, 1026
Incidence assay; 624, 626
Incidence rates; 638
Incident tuberculosis; 938
India; 641, 1016
Indoleamine 2,3-dioxygenase (IDO); 295, 317
Indoleamine 2,3-dioxygenase-1; 899
Inducible HIV-1; 398
Infant; 33, 897, 948
Infant HIV-free survival; 871
Infant TB; 872
Infants; 879, 880, 883, 905
Infection; 600
Infection risk; 862
Infections; 941
Infectivity; 39, 209
Inflammasome; 313, 323
Inflammation; 47, 134, 266, 270, 309, 313, 314, 315, 319, 454, 496, 500, 501, 565, 730, 737, 745, 761, 763, 778, 803, 934, 1050, 1085
Inflammation markers; 738, 772, 797
Inflammatory biomarkers; 312, 756, 810
Inflammatory markers; 305, 491
Infliximab; 813
Influenza vaccination; 947
Influenza vaccine; 342
Ingenol; 416
Inhibitor; 212, 539
Inhibitory receptor; 389LB
Injectable contraception; 28
Injection drug use; 14, 217, 598
Injury; 1055
iNKT cells; 705
Innate immunity; 41, 52, 79, 123, 124, 184, 191, 192, 279, 281, 289, 307, 547, 811
Innate response; 43, 286
Innate-like T cell; 278
Innovative trial designs; 95LB, 131
Inpatient; 1100
Insulin; 880
Insulin resistance; 744, 745, 771, 787, 929
Insurance; 1064, 1066, 1070
Integrase; 540, 591
Integrase Inhibitor (INI); 140, 594, 608, 9851
Integrase mutation; 121
Integrase strand transfer inhibitor; 591, 609, 953
Integrated DNA; 354
Integrated prevention services; 128, 135
Integration; 611
Integration site analysis; 199, 381
Integration sites; 21, 105, 107
Intelligence quotient; 495
Intensification; 549
Interaction; 521
Interferon; 40, 44, 184, 280, 671, 681
- Alfa; 414
- Alpha; 54LB, 186, 217
- Gamma; 281, 313
- Responses; 498
- Stimulate genes; 292

Interferon-free; 649, 691
Interleukin 6; 1049
Interleukin-21; 358
Interleukin-7; 334
International physical activity questionnaire (IPAQ); 489
Internet; 1025
Intimate partner violence; 853, 980
Intravaginal ring; 1107
Intracellular pharmacology; 81, 83, 526
Intrinsic immunity; 194, 386
iPrEx; 977
IRES translation; 412
IRF3; 187
Iron; 461, 567
Isoniazid preventative therapy; 1108
ITPA; 518
IV drug users; 654

– J –

Jaundice; 515

– K –

K65R; 596, 597
Kaplan-Meier; 156
Kaposi sarcoma; 87, 88, 721, 722, 723
Kaposi sarcoma–associated herpesvirus; 87
Kenya; 102, 597, 624, 712, 853
Key populations; 102
Key populations (MSM); 102, 1063, 1063
Kidney; 742
Kidney function; 792, 797
Kidney transplantation; 798, 799
Killer-cell immunoglobulin-like receptor (KIR); 275, 276, 924
Killing; 167
KIR2D; 275
KIR3DL1/S1; 277
KLF2/Statin; 298LB
KSHV; 69
Kynurenine-to-tryptophan (KT) ratio; 295

– L –

L-selectin; 426
Laboratory reporting time; 613
Lamivudine; 542, 566
Late HIV diagnosis; 999, 1001
Late presentation; 911
Late-stage disease; 221
Latency; 371, 387, 394, 403, 412, 413, 416, 418, 423, 428LB
- Models; 390, 424
- Reversing agents; 372, 406, 428LB

Latent; 827LB
- HIV; 376
- HIV-1 reactivation; 391, 397, 417, 419, 421LB
- HIV-1 reservoir; 395, 396
- Reservoir; 392, 397, 427
- Tuberculosis; 817, 885

Latin America; 580
LDV/SOF; 82
Lean mass; 140
Lectin binding; 215
LEDGF; 540
Ledipasvir; 152LB, 689, 692
Lentivirus; 207
Lesotho; 1034, 1103
Leukocyte-endothelial cell interactions; 735
Levonorgestrel; 85LB, 858
LGMD1F; 196
Life expectancy; 161, 1052
LILRA3; 282
Limiting antigen avidity enzyme immunoassay; 625
Linear mixed models; 576
Linkage; 1078
Linkage to care; 29, 99, 100, 154, 632LB, 661, 666, 1005, 1016, 1069, 1074, 1090, 1093, 1097, 1111
Linkage to HIV care; 93
Lipid profile; 930
Lipids; 309, 782, 787
Lipoatrophy; 804
Lipodystrophy; 140, 779, 803
Lipohypertrophy; 804
Liver; 679, 808
- Biopsies; 706
- Cirrhosis; 645
- Disease; 677, 805
- Disease progression; 657, 680
- Fibrosis; 660, 806, 807
- Progression; 636
- Transplantation; 640, 799

Liver-related death; 637
Liver-related endpoint; 671
Local and systemic PK; 524
Long-term nonprogressor; 347
Long-term; 156, 882
Long-term follow-up; 36, 405
Longitudinal; 927, 1068
Longitudinal study; 437
Lopinavir; 588, 960
Lopinavir/ritonavir; 36, 374, 511, 527, 955
Loss to follow-up; 156, 558, 1009, 1077
Low-income countries; 71, 1118
Low-level viremia; 107
LRA; 416
LTBI; 827LB
Lung cancer; 727, 728
Lung function; 490
Lymph node; 188, 188
Lymphocyte activation; 320, 772
Lymphogranuloma venereum; 845
Lymphoid tissue; 325
Lymphoma; 70, 429, 719
Lysosomal integrity; 395

– M –

M2-like macrophages; 677
mAb; 371
mAb combination; 346
Macaque; 363, 433, 476, 510, 966LB
Macaque models; 286
Macrocyclization; 693
Macrophage; 183, 188, 199, 204, 205, 268, 361, 410, 418, 476, 501, 502, 528, 529, 753, 835
- Activation; 676
- Polarization; 61
- Tropism; 440

Magnetic resonance imaging; 935
Magnetic resonance spectroscopy; 441
Maintenance therapy; 551, 554LB
MAIT cell; 278
Malaria; 513, 883
Malawi; 1046
Male circumcision; 30, 1084, 1085, 1086, 1087, 1089
Male partners; 1018
Malnutrition; 876, 915
Mangabeys; 279
Mannose binding lectin; 481
MAP2; 464
Maraviroc; 86LB, 959, 208, 263, 441, 547, 549, 564, 633, 769LB, 814, 950, 959, 960, 964, 965, 993
Marginal structural modeling; 578
Marginalized populations; 245
Marijuana; 1006
Markov model; 97

Maternal TB; 872
Maternal-to-infant transmission; 965
Mathematical model; 532, 675, 1105, 1106, 1112, 1117
Maturation; 42, 538, 539
Maturation inhibitor; 114LB
MazF-T; 402
MBL2/APP; 462
mDC/monocyte; 388
MDR; 537
Measles; 945, 946
Measurement; 976
Measures of HIV-1 persistence; 912
Mechanistically based equation; 863
Mediation; 1049
Medicaid; 1064, 1065
Medical monitoring project; 789
Medication sharing; 988
Medroxyprogesterone acetate; 858
Memory cells; 340, 530
Memory t cells; 382
MEMRI; 504
Men who have sex with men (MSM); 14, 22LB, 23LB, 73, 116, 241, 251, 252, 287, 671, 675, 713, 839, 841, 970, 972, 973, 977, 997, 1016, 1019LB, 1020, 1021, 1024, 1025, 1026, 1032, 1041, 1042, 1058, 1060, 1061, 1062, 1070, 1097, 1098, 1099, 1105, 1115
Menopause; 636
Menstrual cup; 857
Mental health disorders; 694
Mesoamerica; 242
Mesoamerican region; 601
Metabolomics; 497, 498
Methamphetamine; 499
Metropolitan statistical area; 1040
MHC-1; 226, 363
Microbial translocation; 271, 307, 310, 329, 477, 676
Microbicide; 26LB, 208, 287, 350, 963, 979, 993, 994
Microbiome; 897, 1085
Microbiota; 861, 266, 861
Microglial activation; 473, 477
Micronutrients; 567
MicroRNA; 471, 759
MicroRNA29; 296
Microvesicles; 366
Middle-income countries; 1118
Migration; 242, 1034
Minority-resistant variants; 983
Minority variants; 592, 982
miR-155; 385
Missed diagnosis; 33
Mitochondria; 411, 460, 500
Mitochondrial injury; 499
Mitochondrial toxicity; 785
MIV-150; 967
MK-5172; 693
Mobile phone use; 559, 889
Mobile technology; 828LB
Mobile VMMC teams; 1086, 1086
Mobility; 1034
Modeling; 25, 150, 509, 531, 1116, 1119
Modified CD4 T cells; 402
Molecular
- Dynamics; 586
- Epidemiology; 92, 240, 241, 245, 246, 816LB
- Mechanisms; 201
- Modeling; 219

Monitoring; 828LB
Monoamine; 498
Monoclonal antibody; 50
Monocyte; 321, 279, 282, 283, 418, 684, 815
Monocyte activation; 466, 732, 738, 772
Montreal cognitive assessment; 472
Morbidity; 877, 1053
Mortality; 161, 316, 317, 577, 584, 641, 671, 720, 809, 810, 825, 831, 832, 833, 917, 990, 1049, 1081
Mother-to-child transmission (MTCT); 162, 868, 869, 872, 879, 893, 898, 904, 906
Moxifloxacin; 95LB
Mozambique; 873
MRI; 485, 488, 490
mtDNA; 496
Mucosa; 273
Mucosal
- Barrier; 211
- Immunity; 168, 186, 267, 270, 272, 286, 289, 861
- Immunology; 262, 269, 287, 366
- Protection; 357

Multicohort study; 569
Multidrug resistance; 553
Multimorbidity; 764
Multiple risk groups; 1121
Multipurpose prevention technology; 1107
Mutation; 610
Mutation resistance; 564
Mx1; 682
MxA; 296
Mycobacterium avium complex (MAC); 812
Mycobacterium tuberculosis; 309, 818, 819
Myeloid activation; 303Myeloid derived suppressor cells; 301
Myelotoxicity; 544
Myocardial infarction; 748, 749LB

– N –

NA-ACCORD; 996
Nadir CD4; 459, 706
Naive CD4 T cell; 334
Naive patients; 611
NanoART; 529
Nanoformulated antiretroviral therapy (ATV+RTV); 543
Nanomedicine; 542
NAT screening; 1022
Native-like envelope trimers; 164LB
Natural killer cells; 367, 372, 679
Needle-exchange program; 1028
Nef; 189, 226, 227, 228
Negative Regulator; 388
Neisseria gonorrhoeae; 1026
Neopterin; 474
Network biology; 13
NeuroAIDS; 60, 62, 440, 447, 478, 504
Neurocognition; 441, 447, 486
Neurocognitive; 57, 439, 936
- Disorders; 455
- Functioning; 450
- Impairment; 63, 451, 462, 469, 470, 483, 491, 499
- Performance; 442

Neurofilament light chain; 60
Neuroimaging; 60, 447
Neuroimaging trait; 461
Neuroinflammation; 60, 477
Neurologic; 760
Neuronal injury; 481
Neuropathogenesis; 439, 469, 508
Neuropathy; 458
Neuropsychiatric tests; 60
Neuropsychological impairment; 448, 459, 467
Neuropsychology; 468, 488, 935
Neurosyphilis; 479, 840
Neurotoxicity; 478
Neutralization; 170LB, 346, 349, 903
Neutralization response; 343, 347
Neutralizing antibodies; 164LB, 345, 906
Neutralizing antibody; 590
Nevirapine; 36, 542
Nevirapine prophylaxis; 889, 909
Nevirapine resistance; 909
New antiretroviral; 104LB
New oral HCV drugs; 16
Next-generation sequencing (NGS); 254, 255, 256, 257, 258, 593
NF-kappaB; 385
NFkB; 187
NFL; 474
NHANES; 789
NHBS; 850
Nigeria; 558, 1063
Nitric oxide; 500
NK; 372
NK cells; 52, 272, 277, 680
NK-like T cells; 678
NK-pDC crosstalk; 285
NKG2D; 367
NKp46; 367
NKT cell; 278
Nondaily use; 978LB
Non-Hodgkin lymphoma; 720
Nonnucleosides; 551
Non-AIDS malignancy; 728
Non-AIDS mortality; 582, 729
Non–AIDS-defining cancers; 726
Non-B subtype; 201, 595
Non-classical monocytes; 466, 754, 796
Non-communicable diseases; 741
Non-Hodgkin lymphoma; 725, 719, 725
Nonhuman primate neuroAIDS model; 503
Nonhuman primates; 962
Nonnucleoside reverse transcriptase inhibitor (NNRTI); 449, 510, 511, 566, 582, 930
Non-HAND; 471
Nonhuman primate models; 591
Nonhuman primates; 223, 349
North America; 580, 996
Novel diagnostic tests; 621, 826
Novel drugs; 131
nPEP; 958, 958
NRTI; 537, 541, 585, 785, 788
NS5A inhibitor; 696
NS5A mutation; 696
Nuclease; 401
Nucleoside analog; 541
Nystatin; 844

– O –

OAS; 682
Obesity; 763, 778
Observational cohort; 101, 569, 806, 865
Observational studies; 1025
Occult HBV in India; 704
Occupational; 1027
Occupational exposure; 957
OCT1; 519
Older female sex workers; 1030
Older population; 491

On demand; 23LB
Online; 1096
Opportunistic infection; 836, 838, 917
Option B+; 865, 865, 873, 874, 875
Oral candidiasis; 844
Oral fluid; 635
Oral mucosa; 897
Oral shedding; 716
Oral warts; 716
Oraquick; 635
Orphanhood; 1036
Outcomes; 718
Oxidative stress; 306, 501

– P –

p21; 386
P2X; 323
P2X7 ATP receptors; 735
p6; 235
Paediatrics; 916
Panobinostat; 109
Parathyroid hormone; 790
Parental sequences; 231
Partner notification; 1018, 1099, 1105
Partner services; 238, 1003, 1093
Partner testing; 240
Passive infusion; 903
Pathogen-associated molecular pattern; 43
Pathogenesis; 366, 404, 811
Patient follow-up; 1077
Pattern recognition receptor; 43
PCR; 394, 616, 910
PCR free; 258
PCSK9; 731
PD-1; 300
PD1; 389LB
Pediatric; 37, 700, 801, 871, 919, 927, 931, 934, 951, 954
- Adolescents; 38LB
- ART; 914
- HIV; 921, 923, 937, 938, 940, 947

Peginterferon alpha; 695
Penicilliosis; 843
People who inject drugs; 1016, 1116
People who use drugs; 176
PEPFAR; 160
Peptide-MHC tetramer; 362
Pericardial fat; 744
Perinatal; 943
Perinatal HIV exposure; 936
Perinatal HIV infection; 334, 396, 922
Peripheral blood mononuclear cells (PBMCs); 81, 437
Peripheral neuropathy; 457
Persistence; 21, 105, 243, 381, 418, 425, 430, 983
Persistent replication; 706
Persons who inject drugs (PWID); 998
PET; 482
Phage display and rational design; 213
Pharmaceutical use; 1054
Pharmacodynamics; 114LB, 526, 528, 922LB
Pharmacogenetics; 533, 515, 533, 791
Pharmacogenomics; 516, 517, 518
Pharmacokinetics; 82, 85LB, 532, 510, 512, 516, 517, 532, 650, 792, 887, 892, 893, 894, 922LB, 951
Pharmacologic measures; 514
Pharmacology; 436
PHI; 335, 377
Phosphate; 768
Phylodynamic analysis; 249
Phylodynamics; 236, 253
Phylogenetics; 127, 248, 250, 251, 252, 291
- Analysis; 109, 238
- Clusters; 253

Phylogeny; 230, 244, 247
Phylogeography; 229, 236
Physical activity; 489, 745, 804
PI-containing ARV regimens; 82
Pig tailed; 363
Placebo controlled; 139
Placenta; 898
Planned treatment interruption; 919
Plasma cells; 340
Plasma concentrations; 891
Plasma membrane; 45
Plasmacytoid dendritic cell; 186, 225
Platelet function; 732
Platelets; 736
PMTCT; 31LB, 32, 34, 533, 533, 863, 864, 866, 871, 878, 886, 908, 909
PMTCT and option B plus; 78
POC; 114LB
Point of care; 34, 614, 320, 630, 631
Point of care CD4 testing; 632LB, 1090
Policy; 160
Polymorphism; 226, 462, 611
Pomalidomide; 87
Pooling; 616, 619
Pooling PCR; 704
Population; 1038
- Based; 1054
- Based cohort; 159, 740
- Based intervention; 1093
- Effectiveness; 158
- Inference; 255, 255
- Level impact; 25, 158
- Viral load; 32, 153, 328, 1071

Postexposure prophylaxis (PEP); 957, 959, 957, 960, 961
Postpartum; 890, 899, 907
Posttreatment control; 111LB, 377
Practice guidelines; 750, 658, 750
Pre-ART; 573, 1076
Prediction; 343
Predictive value of test; 628
Predictors; 469
Preexposure prophylaxis (PrEP); 8, 20, 22LB, 23LB, 24, 25, 86LB, 128, 514, 946, 962, 969, 970, 972, 973, 974, 975, 976, 977, 978LB, 979, 980, 981, 983, 984, 986, 988, 993, 1083, 1106, 1107, 1115, 1121, 1122
Pregnancy; 28, 85LB, 533, 864, 887, 888, 891, 892, 893, 894, 895, 899, 900, 901, 902, 907, 1108, 1122
Prenylation inhibition; 708LB
PrePex; 1087
Preterm; 878
Prevalence; 452, 697, 856
Prevention; 56, 74, 1104, 157, 160, 734, 966LB, 971, 994, 1023, 1083, 1104
Prevention of mother-to-child transmission (PMTCT); 867, 870, 874, 875, 895, 1122
Primary
- Care; 103LB, 666
- Cells; 187
- HIV infection; 62, 373, 383, 446, 475
- HIV-1 infection; 251
- Immune cells; 527
- Infection; 111LB

Primer ID; 255, 593
Prisons; 807
Profibrotic factors; 796
PROBE-C study; 670
Progesterone; 860, 902
Prognostic; 316
Prognostic model; 1120
Prognostic score; 637
Program effectiveness; 158
Progression; 198
Progression of HAND; 465
Progressive multifocal leukoencephalopathy; 814
Proliferation; 107, 330
PROMISE; 31LB
Prospective; 308, 560
Protease; 42, 588
Protease inhibitor; 551, 566, 582, 604, 644, 693, 699, 733
Proteome; 529
Proteomics; 287, 409
Providers; 974
Proviral DNA; 35, 332
Proviral total DNA; 354
Pseudotyping; 214
Public health; 1024
Pulmonary tuberculosis; 817
Pulse wave velocity; 925, 926
Purinergic; 323
Pyroptosis; 202

– Q –

Q80K; 697
qEEG; 449
Quality of care (QoC); 561, 1077
Quality assurance; 634
Quantification; 421LB
Quantitative digital PCR; 420
QUS; 776
QVOA; 397

– R –

Rab mediated; 543
Rab6A; 195
Raltegravir; 547, 552, 564, 594, 608, 891, 960
Random forest; 331
Randomised controlled trial; 94
Randomised double-blind placebo-controlled trial; 322
Randomised open-label trial; 779
Randomized controlled trial; 1091
Randomized trial; 137
Rapamycin; 415
Rapid diagnostic tests; 621, 629, 826, 1091, 1098
Rapid progressors; 338, 572
RCT; 22LB
Re-engagement in Care; 854
Reinfection; 654
Relinkage; 1074
Reactivation; 395, 409
Readthrough transcripts; 384
REAF; 192, 192
Real-time PCR; 277
Real-time adherence monitoring; 8, 556, 559
Rebound virus; 112LB
Recency of HIV Infection; 603, 625, 626, 627
Recombinants; 232
Recombination; 231, 257, 424
Record linkage; 724
Recreational substance use; 743
Rectal; 994
- Gels; 993

- Infection; 324
- Microbicides; 269
- Squamous cell carcinoma; 717
- Tissue; 964

Recurrence; 830
Regression discontinuity; 1110
Regulatory T cells; 284, 325, 326, 353, 819, 900
Relapse; 681
Remission; 373
Renal; 511
- Biopsy; 794
- Failure; 642
- Function; 793, 934
- Impairment; 795
- Insufficiency; 781, 781
- Tubular disease; 143LB, 794

Repeat testing; 1022
Repertoire; 355
Replicating effectiveness programs; 7
Replication; 394
Replication-competent reservoir; 414
Reproductive; 896
Reproductive hormone; 862
Reservoir; 21, 110LB, 374, 394, 423, 425
Residual viremia; 105, 168, 379, 389LB
Resistance; 537, 596, 603, 696, 699
- Associated variants; 698
- Haplotypes; 593
- Mutations; 590
- Testing; 119
- Mutants; 589
- Mutation; 540

Resource Limited Settings; 156, 451, 459, 557, 571, 574, 604, 619, 779, 832, 920, 932, 1011, 1013, 1015, 1073, 1120
Respiratory isolation; 824
Resting T cells; 426
Restriction factor; 122, 190, 203, 204
Retention; 577, 584, 875, 1072
Retention in care; 100, 854, 890, 996, 1004, 1012, 1068, 1073, 1075, 1092
Retrovirus; 45
Return to care; 1002
Rev; 104LB, 201
Revaccination; 946
Reverse transcriptase; 255, 585
Reverse transcription; 200
Rhesus macaque; 50, 406, 965
Ribavirin; 691
Ribavirin triphosphate; 518
Rifabutin; 940
Rifampicin; 532
Rifampin; 521
Rifapentine; 827LB
Rilpivirine; 554LB, 605, 737, 894
Risk; 1014
- Behavior; 850, 1018, 1021, 1022, 1024, 1058
- Compensation; 1088
- Factor analysis; 674
- Factors; 297, 469, 713, 843, 1024
- Prediction; 88, 747, 751, 1017
- Score; 1017

Risky sexual behavior; 1039
RITA; 1042
Ritonavir-boosted lopinavir; 930, 956
Ritonavir-boosted protease inhibitor; 793
RNA; 42, 618
- Packaging; 45
- Seq; 11, 258
- Splicing; 104LB

Romidepsin; 406
Rosuvastatin; 733, 771
Routinely collected clinical markers; 619
RT-PCR; 420
RT/HBsAg variability; 702
Rural; 558
Rural Uganda; 458
RV144; 170LB
Rwanda; 157, 780, 865, 1109
Rwanda Military Hospital; 700

– S –

Safer conception; 895
Safety; 940, 954
SAHA; 407, 408, 409
SAMHD1; 203, 202, 202, 203, 205, 206, 207
Sample-to-cutoff ratio; 627
Sanctuary sites; 534
Saporin; 362
Saturation mutagenesis; 216
Scale-up; 175, 176, 1114
sCD14; 47, 268, 547, 778, 899
sCD163; 303, 316, 319, 676, 784, 806, 1050
School enrollment; 1036
Sclerostin; 767
Screen; 40
Screening; 90, 455, 658, 668, 710, 712, 727, 823
Second line; 457, 563
Second-line antiretroviral treatment; 782, 571, 782, 956
Second-line regimens; 552, 779
Second-line therapy; 119
Selection bias; 1102
Selenium; 567
Self-report; 555, 977
Self-reported condom use; 1030
Self-selection; 1088Self-testing; 634, 1103
Semen; 208, 209, 366
Semenogelin; 209
Senescence; 300
Sensitive testing; 982
Sequencing; 699
Sequential envs; 344
Serious adverse events; 648, 648
Seroconverters; 97, 602, 986
Serodiscordance; 314, 895, 1122
Serodiscordant couples; 969, 1035
Seroprevalence; 98, 667
Serosorting; 1062, 1063
Serum cholesterol; 781
Services; 1067
Set-point viral load; 1048
Severe immunodeficiency; 913
Severe non-AIDS events; 271, 562
Sex; 558
Sex workers; 853, 1031
Sexual
- Behavior; 1060, 1060
- Event coverage; 978LB
- Positioning; 1063, 1063
- Risk behavior; 972, 1036, 1061
- Transmission; 214, 674, 1029

Sexually transmitted disease; 1047
Sexually transmitted infection (STI); 304, 568, 944, 962, 963, 1032, 1033, 1099
Shedding; 855
SHIV; 50, 344, 433
Shock and kill; 387
Short cycle therapy; 38LB
shRNA screen; 46LB
Side effects; 888
Sieve analysis; 55LB, 349
Siglec-1 (CD169); 283
Simeprevir; 149, 644, 645, 647, 648, 652
Simian foamy virus; 237
Simplification; 553
Single
- Cell; 11
- Cell analysis; 421LB
- Nucleotide polymorphism; 516
- Genome sequencing; 106, 396
- Round virus; 424
- Variant sequencing; 686

siRNA; 205
SIV; 108, 192, 203, 268, 286, 298LB, 324, 349, 361, 363, 370, 406, 416, 476, 503, 591, 948, 965, 966LB
SIV/HIV chimeric viruses; 280
Skin; 941
Skin and soft tissue infections; 847
SLC22A1; 519
Sleep quality; 937
Smoking; 726, 727, 728, 743, 763, 901
Smoking cessation; 139
SNP; 682
Social; 74
Social media; 1098
Socioeconomic status; 560, 1036
Sofosbuvir; 148, 149, 151LB, 152LB, 644, 645, 646, 647, 648, 650, 652, 689, 692
Sofosbuvir phosphates; 81
Soluble CD163; 316, 744, 753
Soluble CD40 ligand; 284
South Africa; 26LB, 89, 92, 93, 724, 1110, 603, 724, 852, 921, 1033, 1080, 1091, 1110
Southern Africa; 718, 938
SPARTAC; 111LB
Spatial analysis; 991LB
Spatial mapping; 1045
Spirometry; 800
Spix's owl monkey; 223
SQ109; 95LB
Staphylococcus aureus; 846, 847
STAT5; 183
Statins; 136, 137, 502, 643, 734, 771
Statistical interaction; 562
Statistical power; 9
Stavudine; 781
Stem-cell transplantation; 430
Stigma; 1057, 1058, 1059
Stillbirth; 878
Strategies; 1079
Stribild; 113LB
Stroke; 760
Structure; 412
Study design; 9
Subepidemic; 247
Sub-Saharan Africa; 32, 781, 73, 115LB, 118, 153, 161, 570, 583, 624, 634, 711, 719, 721, 762, 781, 807, 874, 1071, 1073, 1075, 1090, 1101
Subgroups; 550
Substance use disorders; 804
Subtype; 201, 596, 622
Subtype B; 229
Subtypes; 633
Sulfamethoxazole; 512

Superinfection; 259, 869
Suppression; 1023
Suppressive ART; 491
Surveillance; 234, 239, 601, 603, 607, 729, 1043, 1115
Surveillance data; 1001, 1064
Survival; 97, 578, 711, 1051, 1110, 1119
Sustainable; 1067
Sustained virologic response (SVR); 149, 643, 653, 654, 656, 657, 942
Symptomatic acute HCV infection; 14
Symptoms; 855, 1044
Synergy trial; 148
Syphilis; 304, 304, 839, 840, 841, 842, 848
Syrup; 955
System gaps; 911
Systems biology; 269

– T –

T cell; 46LB, 185, 210, 273, 284, 946
- Activation; 266, 267, 317, 928
- Exhaustion; 172
- Immunity; 281
- Receptor; 365
- Subsets; 267

T follicular; 166
T stem cell memory; 53
T-bet; 172
T-regulatory cells; 817
Tablets; 955
TAF; 113LB, 530
Tanzania; 606
Taq polymerase; 255
Targeted mutagenesis; 400
Targeted testing; 668
TasP; 24, 1115
Tat; 505
Tat inhibitor; 413
Tat mRNA; 412
TCA; 497
TCR Cloning; 365
TDR; 608
Telomere; 901
Telomere length; 306, 784, 881, 923
Temporal trends; 602, 729
Tenofovir; 23LB, 27, 113LB, 269, 511, 516, 517, 530, 596, 597, 765, 767, 768, 788, 791, 792, 794, 879, 953, 971, 986, 993, 994
- Alafenamide; 143LB, 795, 952
- Detection; 979
- Disoproxil fumarate; 143LB, 790, 793, 954, 981, 992LB
- Gel; 26LB, 27, 982, 984
- PrEP; 984, 987
- Sparing; 766

Tenofovir/emtricitabine; 83, 525, 526, 566, 962, 972, 975
Test-seeking behavior; 1010
Testes; 534
Testing; 628, 1014, 1066, 1082, 1096, 1113
Tetherin; 122
Text message; 559
Tfh; 206, 947
Tfh cells; 49, 166, 326
TFV vaginal gel; 963
TFV-DP; 530
Th17; 206, 274
Th17 cells; 329
Thailand; 275, 276, 511
THC; 639
The Veterans Aging Cohort Study index; 467
Therapeutic drug monitoring; 956
Therapeutic vaccine; 352
Therapy; 646, 646
Thrombocytopenia; 476
Thymus; 922
Time from HIV infection to viral suppression; 99
Time of infection; 599
Time to ART initiation; 581, 632LB
Tissue; 425
- Factor; 268
- Macrophages; 380
- Resident; 425

TLR; 183
TLR7; 417
TLR8; 282
TMAO; 755, 758
TNPO3; 196
Tolerability; 957
Topical PrEP efficacy; 963
Total DNA; 376
Toxicity; 792
TRAIL; 285
Trajectory; 494
Transinfection; 46LB
Transcription; 413
Transcriptional networks; 172
Transcriptionally active proviruses; 912
Transcriptome; 324, 326
Transduction; 207
Transgendered; 1032
Transition to adult units; 918
Transmission; 209, 215, 217, 243, 247, 248, 250, 254, 672, 868, 869, 1115
- Biology; 126
- Cluster; 245, 246, 598
- Network; 120, 239, 240, 246
- Risk; 101, 816LB

Transmitted drug resistance; 598, 599, 600, 601, 607
Transmitted founder; 44
Transmitted founder virus; 288, 364
Transmitted founder HIV-1; 54LB, 223
Transplantation; 70, 432
Transport; 519
Treatment; 78, 1114, 181, 690, 715, 828LB, 1023, 1114
- Access; 641
- As prevention; 27, 128, 180, 244, 989, 991LB, 1095, 1118
- Continuum; 1006, 1070
- Experienced; 545, 644
- Failure; 571, 617, 1120
- Interruption; 110LB, 111LB, 1011
- Naive adults; 445, 550
- Outcomes; 659
- Response; 842

TREG; 274, 290
Trends; 850, 1060
TRIM32; 385
Trimethoprime; 512
Trimethylamine; 138
Tropism; 112LB, 219, 336, 564, 633
Truvada; 962
Tuberculosis (TB); 91, 130, 131, 810, 811, 813, 816LB, 821, 823, 825, 826, 827LB, 828LB, 829, 830, 831, 939, 940, 1108
- Diagnosis; 824
- In pregnancy; 822
- And HIV; 92, 822
- Meningitis; 826
- Prophylaxis; 115LB

TURQUOISE-I; 147
Type 1 interferon; 124, 188, 225, 292, 898
Type 2 diabetes; 758, 803

– U –

UDL; 117
Uganda; 30, 317, 452, 454, 577, 1037, 1039, 1067
UGT1A1; 515
Ukraine; 1042
Ultradeep sequencing; 702, 785, 983
Ultrasensitive viral load; 564
Ultrasound; 932
UNAIDS 90-90-90; 1071
Undetectable HIV viral load; 438
Undiagnosed; 667
Undiagnosed HIV; 98, 1013, 1117
United States; 1052, 1057, 1060
Unplanned ART interruptions; 1015
Unprotected intercourse; 1024
Untranslated region; 169
Urine tenofovir assay; 975
URMC-099; 543
USA; 116, 242

– V –

Vaccination; 353, 701, 945
Vaccine; 55LB, 64, 66, 163, 349, 905, 948
Vaccine response; 318
Vaccines; 216, 370
VACS; 487
VACS index; 746
Vaginal ring; 524, 992LB, 995
Varenicline; 139
Vascular; 475
Vascular disease; 760, 926
Vascular toxicity; 735
vCCL2 N-terminus peptide; 213
Verbal autopsy; 825
Vertical transmission; 937, 942
Vertically HIV-infected; 918
Veterans; 750, 750
VIA; 710
Vif; 193
VIH-1; 193
Violence; 102
Viral
- Decay; 548
- Diversity; 612
- Fitness; 119
- Hepatitis; 708LB
- Kinetic modeling; 148
- Kinetics; 393
- Load; 51, 864, 235, 314, 614, 617, 689, 841, 864, 886, 1023
- Load monitoring; 563, 619
- Persistence; 399
- Rebound; 58, 110LB, 168, 556, 560
- Replication; 49, 54LB
- Reservoir; 108
- RNA biogenesis; 104LB
- Sequences; 378
- Suppression; 98, 100, 154, 864, 294, 729, 854, 864, 887, 890, 996, 997, 1056, 1064, 1068, 1069

Viremia; 1004, 1049
Viremia copy years; 562
Virologic

- Control; 1009
- Failure; 118, 559, 956, 990
- Response; 373
- Suppression; 546

Virus assembly; 42, 45
Visconti; 52
Visual inspection; 89
Visuospatial; 468
Vitamin A; 567
Vitamin B; 567
Vitamin D; 308, 787, 790, 791, 931
Vitamin D binding protein; 790
VL time courses; 863
VMMC; 175
VMMC and HIV; 1086
VMMC service delivery modalities; 1086
Vorinostat; 404, 409
Vpr; 41, 224LB
Vpu; 40, 187, 189
Vpx; 203, 203
Vulnerable populations; 513, 1025

– W –

Week 96; 550
Weight gain; 782
West Africa; 236, 576
White matter abnormalities; 935
WHO; 1079
WHO guidelines; 577
Whole exome sequencing; 294
Wnts; 508
Women; 26LB, 780, 100, 636, 775, 780, 850, 896, 1031, 1033, 1050
Wound healing; 30

– X –

X-linked inhibitor of apoptosis; 387
Xpert MTB/RIF; 91, 824

– Y –

Yellow fever vaccine; 318
Young; 839
Young adults; 928
Young black MSM; 1018, 1041
Youth; 450, 936

– Z –

Zidovudine; 871
Zinc finger nucleases; 400, 433